Advisory Committee Briefing Document

Cardiovascular Safety of Rosiglitazone

Endocrinologic and Metabolic Drugs Advisory Committee

Drug Safety and Risk Management Advisory Committee

Meeting on July 13-14, 2010

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LIST ABBREVIATIONS

AE	Adverse event
ACR	Albumin creatinine ratio
ACS	Acute Coronary Syndrome
BARI 2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
BID	Twice a day
BMI	Body mass index
BP	Blood Pressure
CABG	Coronary artery bypass graft
CEC	Clinical endpoint committee
CEVA	Clinical endpoint validation and adjudication
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
CRP	C-reactive protein
CSR	Clinical study report
CV	Cardiovascular
dL	Deciliter
DCCT	Diabetes Control and Complications Trial
DM	Diabetes mellitus
EU	European Union
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good clinical practice
GLIB	Glibenclamide (glyburide)
GLIC	Gliclazide
GLIM	Glimepiride
GLIP	Glipizide
GLY	Glyburide (glibenclamide)
GSK	GlaxoSmithKline
HbA1c	Glycated hemoglobin A
HCP	Healthcare provider
HDL-c	High density lipoprotein-cholesterol
HR	Hazard ratio
ICH	International Conference on Harmonization
ICT	Integrated clinical trials
IDMC	Independent Data Monitoring Committee
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHD	Ischemic heart disease
IMT	Intimal medial thickness
INS	Insulin
IP	Insulin-providing
IRB	Institutional Review Board

IS	Insulin-sensitizing
ITT	Intent-to-treat
IVUS	Intravascular ultrasonography
LOCF	Last observation carried forward
LDL-c	Low density lipoprotein-cholesterol
m	Meter
MACE	Major adverse cardiovascular event
MCP	Monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
MET	Metformin
mg	Milligram
MI	Myocardial infarction
MOA	Mechanism of action
MMP	matrix metalloproteinase
NA	Not applicable
NHANES	National Health and Nutrition Examination Surveys
NHLBI	National Heart Lung and Blood Institute
NIH	National Institutes of Health
NYHA	New York Heart Association
OR	Odds ratio
PAI	Plasminogen activator inhibitor
PI	Package insert or prescribing information
PIL	Patient information leaflet
PIO	Pioglitazone
PRO	Patient-reported outcomes
QD	Every day (once a day)
QOL	Quality of life
RAMI	Ramipril
RR	Risk ratio
RSG	Rosiglitazone
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SU	Sulfonylurea
SVG	Saphenous vein graft
T2DM	Type 2 diabetes mellitus
TIA	Transient ischemic attack
TID	Three times a day
TZD	Thiazolidinedione
U	Units
UKPDS	United Kingdom Prospective Diabetes Study
US	United States
USPI	US Prescribing Information
VADT	Veterans Affairs Diabetes Trial

Trademark Information

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AVANDIA	None

EXECUTIVE SUMMARY

Background: The FDA has re-convened a Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee to review the totality of new and existing cardiovascular safety data on AVANDIA® (rosiglitazone maleate) Tablets since these committees met in July 2007.

Following the 2007 Advisory Committee Meeting, additional cardiovascular safety data on rosiglitazone (RSG) have become available from a number of sources: meta-analyses, observational studies, and controlled trials.

Meta-analyses: GlaxoSmithKline (GSK) conducted an updated integrated clinical trials (ICT) analysis incorporating 10 new studies into the prior 42-study ICT. This 52-study ICT analysis did not show a significant difference between RSG and control for myocardial ischemic events (hazard ratio 1.098 [95% CI 0.890, 1.354, p=0.38]). This result is in contrast with the result from the 42-study analysis with a hazard ratio for the myocardial ischemic events of 1.30 [95% CI 1.004,1.685, p=0.047], available at the time of the July 2007 Advisory Committee meeting. The change in the hazard ratio between the 42-study and the 52-study datasets indicates the instability of any of the hazard ratios determined using this methodology, particularly when the event rate is low and the confidence intervals are relatively wide. Given these mixed results, randomized clinical trial data are required to further inform on the cardiovascular safety of RSG.

Observational studies: A number of observational studies have been conducted to evaluate the occurrence of major cardiovascular events during treatment with a thiazolidinedione (TZD) (RSG or pioglitazone [PIO]) . GSK has comprehensively reviewed the literature on observational cardiovascular studies that have been published since June 2007 in which RSG was studied. Twenty-one such studies were identified that constitute a much larger dataset than the dataset available in 2007, which did not show an increase in CV risk with RSG. The new observational studies varied by design, length of time of observation, the duration of diabetes for an individual, the definition of cardiovascular events, the medications investigated and the comparisons made. In studies comparing RSG to other anti-glycemic agents, six studies showed no statistically significant difference in the risk of myocardial infarction for RSG compared to other anti-glycemic agents while three studies showed a statistically significant increased risk of myocardial infarction for RSG. However, there was no increased risk of cardiovascular mortality or all cause mortality. In those observational studies that directly compared rosiglitazone to pioglitazone, the majority (n= 7) of studies showed no statistically significant difference in the risk of myocardial infarction between rosiglitazone and pioglitazone; others (n=3) showed that the point estimate favored pioglitazone compared to rosiglitazone, and one study had mixed results depending on the medication based strata examined. Only direct head-to-head comparisons in prospective randomized-controlled trials enable widely convincing conclusions about the comparability of RSG and other anti-glycemic agents.

Controlled CV outcome clinical trials: Since 2007, final data have become available from several large long-term cardiovascular outcome studies. The RECORD study, an open label, large, long-term, prospective, randomized, controlled trial in 4,447 type 2 diabetic patients, was designed to evaluate cardiovascular (CV) outcomes for RSG vs metformin (MET) and sulfonylurea (SU). With a total of 644 primary events, RECORD achieved its primary endpoint, according to its pre-specified non-inferiority margin of 1.2 [hazard ratio 0.99 (95% CI 0.85-1.16)]. In addition, the result for the secondary endpoint of major adverse cardiovascular event (MACE) was 0.93 (95% CI 0.74-1.15). This study demonstrated the non-inferiority of RSG compared to MET and SU on the combined outcome of CV death and CV hospitalization.

Additional supportive data for cardiovascular safety comes from the National Institutes of Health (NIH) sponsored BARI 2D study. BARI 2D is a large, long-term, prospective, randomized, controlled trial in 2,386 patients with type 2 diabetes and stable coronary artery disease. A post-hoc analysis conducted by NIH of RSG treated patients in the study did not show an increased risk for all cause mortality, MACE, or myocardial infarction (MI). These results are consistent with the primary result from RECORD showing no increase in overall CV risk.

Glycemic efficacy: Rosiglitazone has demonstrated glycemic efficacy, both in the short-term, with up to 1.5% reduction in glycated hemoglobin A (HbA1c), and in the long-term, showing more durable glycemic control compared to MET and SU in two long-term studies (ADOPT and RECORD). Short- and long-term reductions in microalbuminuria have been demonstrated with RSG treatment. In RECORD there was no increase in microvascular complications compared to MET and SU, agents that have demonstrated reductions in microvascular events in the United Kingdom Prospective Diabetes Study (UKPDS) study.

Safety profile: Rosiglitazone has been extensively studied, both before and following approval, and its safety profile is well characterized. The association of RSG with fluid retention and congestive heart failure (CHF), which are recognized TZD class effects, was well characterized from short-term studies. Another TZD class effect, increased risk of fracture, only became apparent initially in long-term RSG studies but has now been included in labeling for both RSG and pioglitazone (PIO).

Comparison of rosiglitazone vs. pioglitazone: There are no completed large, long-term, head-to-head randomized clinical trials comparing RSG and PIO. A recent Science Advisory from the American Heart Association and American College of Cardiology Foundation entitled "Thiazolidinedione Drugs and Cardiovascular Risks" summarized the available data concerning TZDs and cardiovascular risk, with a focus on ischemic heart disease (IHD) events. It concluded that there is no reliable evidence to support the choice between RSG and PIO [Kaul, 2010]. The TIDE study (Thiazolidinedione Intervention and vitamin D Evaluation), an FDA post-marketing requirement, was initiated after the 2007 Advisory Committee Meeting and will provide a head-to-head randomized comparison of RSG and PIO. TIDE has been approved by the majority of Institutional Review Boards (IRBs) and Ethics Committees around the world who have thus far reviewed the protocol. GSK remains committed to the successful conclusion of the TIDE study.

Summary and conclusion: Taken together, the totality of the data from ICT, observational, and large controlled clinical studies continue to support the overall positive benefit risk profile of RSG as an important medicine for type 2 diabetes mellitus (T2DM) patients. Better durability of glycemic control with RSG compared to both SU and MET has been demonstrated in two long-term studies. This durability benefit has the potential, in real life conditions, to reduce microvascular complications of type 2 diabetes and to avoid the need for additional therapy, including insulin. Treatment with RSG does not demonstrate an increased risk in macrovascular complications compared to MET and SU. Therefore, the overall benefit risk profile for RSG remains positive.

1. INTRODUCTION

On July 30, 2007, FDA hosted a Joint Public Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee to discuss the cardiovascular safety data on rosiglitazone (RSG), in particular myocardial ischemic events. The Advisory Committees considered the available data from meta-analyses, observational studies, and from long-term clinical trials ADOPT and DREAM, and an interim analysis of RECORD. The Minutes of the Advisory Committee Meeting captured the comments of the Committee on the two voting questions (Appendix 1). For the first voting question, "Do the available data support a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes mellitus?", the vote was 20 "Yes" and 3 "No". The minutes reflect the reluctance of many of the committee members to draw conclusions based on the available data which they indicated could be categorized as "suggestive of" rather than "evidence of" increased cardiac ischemic risk. For the second voting question "Does the overall risk-benefit of Avandia support its continued marketing in the US?", the vote was 22 "Yes" and 1 "No".

In November 2007, FDA approved revisions to the US Prescribing Information (USPI) of Avandia Tablets to reflect both the available data on the risk of myocardial ischemia during treatment with RSG and the absence of CV outcome data for any anti-glycemic agent. The revised USPI included prominent text regarding myocardial ischemia in the boxed WARNING, as well as detailed information in the WARNINGS and PRECAUTIONS, to summarize the data on myocardial ischemic events from a 42 study meta-analysis of 14,237 subjects and from three long-term trials including 14,067 subjects. The overall conclusion, stated in the prescribing information was that "the available data on the risk of myocardial ischemia are inconclusive". The current approved US label for Avandia Tablets is included in Appendix 2.

Since the July 30, 2007, Advisory Committee Meeting, additional cardiovascular safety data on RSG from several large long-term CV outcome trials has become available (RECORD, BARI 2D, ACCORD, VADT). In particular, RECORD is the prospectively designed study to evaluate RSG on CV outcomes in patients with type 2 diabetes mellitus (T2DM). None of the data from any of these studies support the hypothesis raised by the 42-study meta-analyses, nor does an updated GSK-conducted integrated meta-analysis comprising 52 studies with RSG. GSK submitted a supplemental New Drug Application to FDA in August 2009 with proposed revisions to the US label to reflect the final results of RECORD to further inform prescribers on the cardiovascular safety of RSG. Based on this larger body of evidence, GSK continues to believe that when used in appropriate patients the benefit risk profile for RSG is positive.

The FDA has reconvened the joint Committees to review the totality of new and existing CV safety data on RSG and to provide an updated assessment of the risks and benefits of RSG in the treatment of T2DM. This Briefing Document summarizes key background information on RSG in the treatment of T2DM and discusses the totality of the existing CV safety data on RSG for discussion at this Advisory Committee Meeting.

2. BACKGROUND OF ROSIGLITAZONE

2.1. Diabetes Background

T2DM is a growing public health problem worldwide. The increasing incidence and prevalence of T2DM is seen in virtually all ethnic and racial groups, worldwide 171 million persons were estimated to have T2DM in 2000 with this number projected to increase to 366 million by 2030. In the United States, approximately 24 million people are affected (CDC 2007), representing an increase of almost 3 million in approximately two years. The epidemic of T2DM is closely associated with an increasing incidence of obesity, which together with associated insulin resistance are key risk factors for the development of the disease. T2DM is characterised by hyperglycemia due to a relative insufficiency of insulin and presents a major health risk to the individual, particularly with regard to chronic risks of both micro- and macrovascular disease. In most countries diabetes is among the top 5 causes of death [Zimmet 1997], with CV disease being the most common cause of mortality in diabetic patients.

All anti-hyperglycemic agents lower glucose and are approved for use based on achieving a clinically meaningful reduction in glycated hemoglobin A (HbA1c). A major challenge in diabetes management is to lower glucose, without causing hypoglycemia, and to maintain glycemic control over the lifetime of the patient. As people are developing T2DM at younger ages, glycemic control needs to be maintained over several decades of life. The UKPDS study [UKPDS 33, 1998] demonstrated the inexorable progression of T2DM over time despite intensive efforts to maintain near normal glycemia with a single agent. With each of the 3 therapies used in the United Kingdom Prospective Diabetes Study (UKPDS) trial (metformin [MET], sulfonylurea [SU] and insulin), there was an initial reduction of glucose toward the target of normoglycemia, but over time there was a need to intensify therapy, either by the addition of another oral agent or an increase in insulin dose, due to a progressive rise in HbA1c.

Therefore, the aim of hyperglycemic therapy is to lower glucose, maintain glucose control over time, and reduce and prevent microvascular complications without a detrimental effect on macrovascular complications. Rosiglitazone maleate (AVANDIA®) is a potent and orally active anti-hyperglycemic compound of the TZD chemical class. As described in this document, RSG has been shown to reduce hyperglycemia and maintain glucose control longer than metformin or sulfonylurea, with no overall increase in cardiovascular morbidity and mortality as compared to these agents.

2.2. Rosiglitazone Effects on Glycemic Control

It has been well established that long-term lowering of glucose has benefits on microvascular complications [UKPDS 33, 1998] (Diabetes Control and Complications Trial [DCCT, 1993]). In clinical studies, treatment with RSG resulted in clinically significant improvements in glycemic control, as measured by fasting plasma glucose (FPG) and HbA1c, with a concurrent reduction in hyperinsulinemia as measured by circulating levels of insulin and C-peptide. This is consistent with the mechanism of action of RSG as an insulin sensitizer to reduce insulin resistance. RSG has been shown consistently to improve a measure of beta cell function (using the homeostasis model of

assessment). Short-term improvement in glycemic control with RSG is consistent with the efficacy seen with other oral anti-hyperglycemic agents. In the long-term, RSG monotherapy has demonstrated more durable glycemic control than monotherapy with MET or SU. Long-term data with newer classes of anti-hyperglycemic agents are currently lacking.

RSG is an effective glucose-lowering agent when given as monotherapy [Charbonnel, 1999], in dual or triple combination with a sulphonylurea [Wolffenbuttel, 2000] and/or MET [Fonseca, 2000] or in combination with insulin [Raskin, 2001]. The addition of RSG to other agents resulted in significant reductions in hyperglycemia compared to the agents alone. These results are consistent with an additive effect on glycemic control when RSG is used in combination therapy.

2.2.1. Short-term Glycemic Control

The glucose-lowering efficacy of RSG monotherapy has previously been demonstrated in six double-blind trials in 2315 subjects with type 2 diabetes previously treated with diet alone or anti-glycemic medication(s). In the two 26-week studies, 1401 subjects with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL [101 to 425 mg/dL] and mean baseline HbA1c 8.9% [5.2% to 16.2%]), treatment with RSG produced statistically and clinically significant decreases in HbA1c (up to -1.5%) and FPG (decreases up to -76 mg/dL).

The efficacy of RSG as additive therapy to MET has been demonstrated in three 26-week, double-blind studies that included 784 subjects with T2DM inadequately controlled on a maximum dose (2.5 g/day) of MET. RSG in combination with MET demonstrated statistically and clinically significant reductions in mean HbA1c (ranging from -0.8% to -1.4%) and FPG (ranging from -40 to -62 mg/dL) compared to subjects continued on MET monotherapy.

The combination of RSG with SUs has been evaluated in a total of 3457 patients in eleven 24- to 26-week randomized, double-blind, placebo/active-controlled studies and one 2-year double-blind, active-controlled study. In the short-term studies, the addition of RSG 4 mg or 8 mg daily to an SU improved glycemic control compared to SU monotherapy or further up-titration of the SU. The addition of RSG to SU resulted in statistically and clinically significant reductions in HbA1c of 0.55% to 1.4% and FPG from 18 to 71.5 mg/dL compared to SU.

In two double-blind studies, triple combination of RSG (4 mg/day and 8 mg/day) with MET and SU demonstrated statistically and clinically significant reductions in HbA1c compared with the use of MET+SU only (ranging from -0.6 to -1.1%) [Dailey, 2004].

RSG (2 mg, 4 mg and 8 mg) in combination with insulin has been evaluated in three randomized, double-blind, controlled studies in 1166 subjects with T2DM inadequately controlled on a standardized twice daily insulin monotherapy. Compared to insulin monotherapy, 4 to 8 mg/day RSG added to insulin demonstrated statistically and clinically significant reductions in HbA1c (-0.4 % to -1.3%). Approximately 40% of all patients reduced their insulin dose when RSG was added.

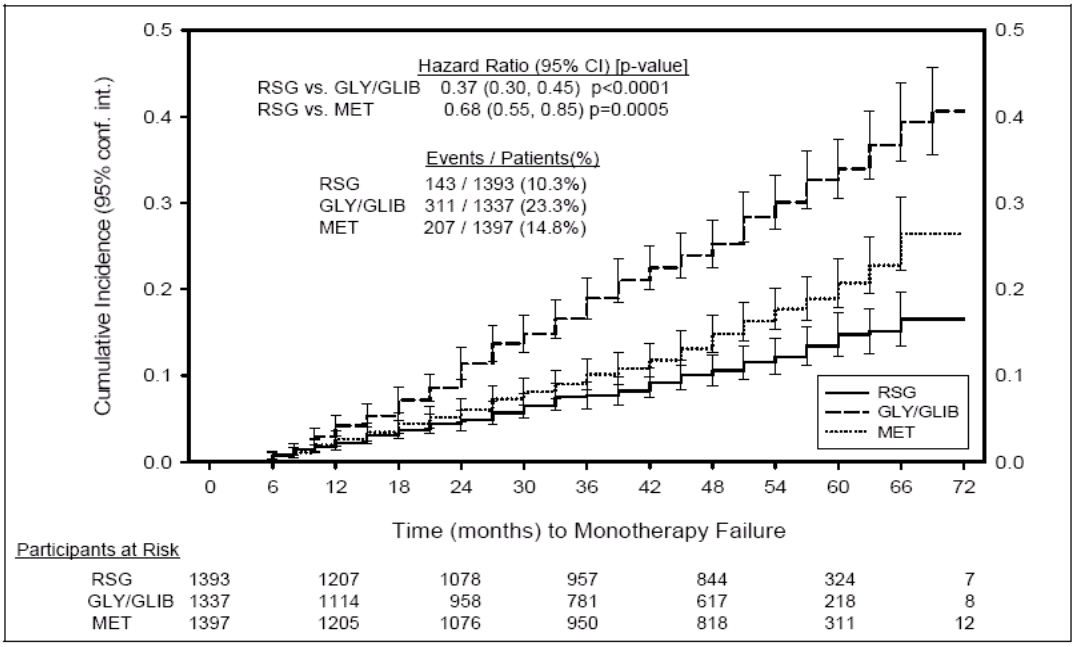
In conclusion, treatment with RSG has been demonstrated in a comprehensive series of clinical studies to produce clinically important improvement in glycemic control, as measured by FPG and HbA1c. Postprandial glucose as well as insulin and C-peptide were also reduced, consistent with the mechanism of action of RSG as an insulin sensitizer. The addition of RSG to either MET or SU resulted in significant reductions in hyperglycemia compared to either of these agents alone. These results are consistent with an additive effect on glycemic control when RSG is used as combination therapy.

2.2.2. Long-term Glycemic Control

The importance of achieving and maintaining normoglycemia continues to gain widespread recognition due to its impact on reducing the risk of long-term complications of diabetes. UKPDS [UKPDS 33, 1998] demonstrated that MET and SU could not maintain glycemic control throughout the course of the study. The first study to show evidence of long-term durable anti-hyperglycemic efficacy of RSG was ADOPT [Kahn, 2006]. This study in patients with newly diagnosed T2DM investigated the efficacy of RSG directly compared to the effect of MET and SU in maintaining fasting blood glucose levels over a median of four years. The primary endpoint of the ADOPT study was the time to monotherapy failure while on maximal tolerated dose of randomized study medication.

Over the 4 to 6 year period of ADOPT, RSG provided the best long-term glycemic control, as evidenced by time to monotherapy failure, HbA1c and FPG, compared to either MET or SU. In ADOPT, RSG significantly reduced the risk of reaching monotherapy failure by 63% relative to SU and by 32% relative to MET during the course of the study, thus demonstrating a greater benefit in maintaining glycemic control relative to both MET and SU (Figure 1).

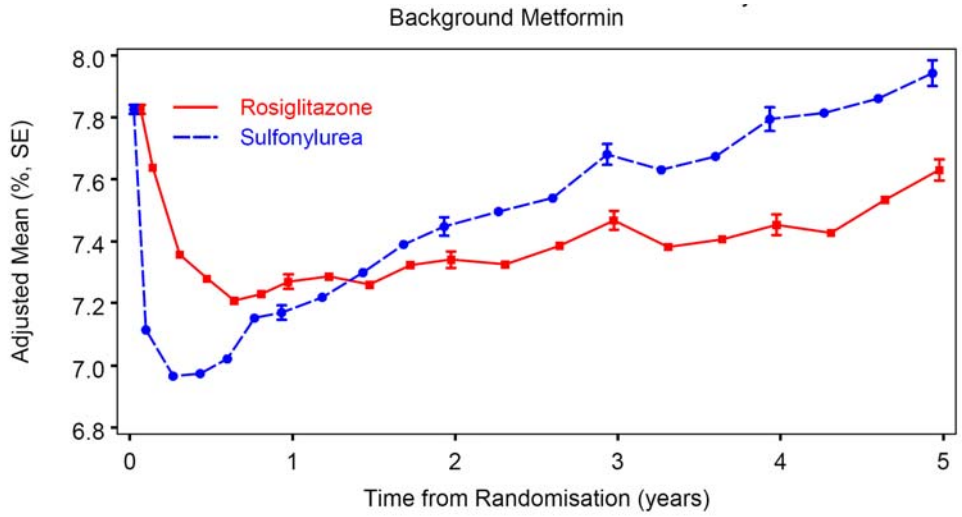
Figure 1 Cumulative Incidence of Monotherapy Failures in ADOPT (ITT Population)



In ADOPT, at 4 years, significantly more patients were adequately controlled (HbA1c <7% or ≤6.5%) with RSG (40% and 26%) than with either SU (26% and 18%, p<0.0001 for both) or MET (36%, p=0.0224 and 23%, p=0.0383). The findings that RSG treatment allows more patients to reach and maintain glycemic targets than SU or MET support the proposition that RSG therapy may delay or avoid the complications associated with poor glycemic control.

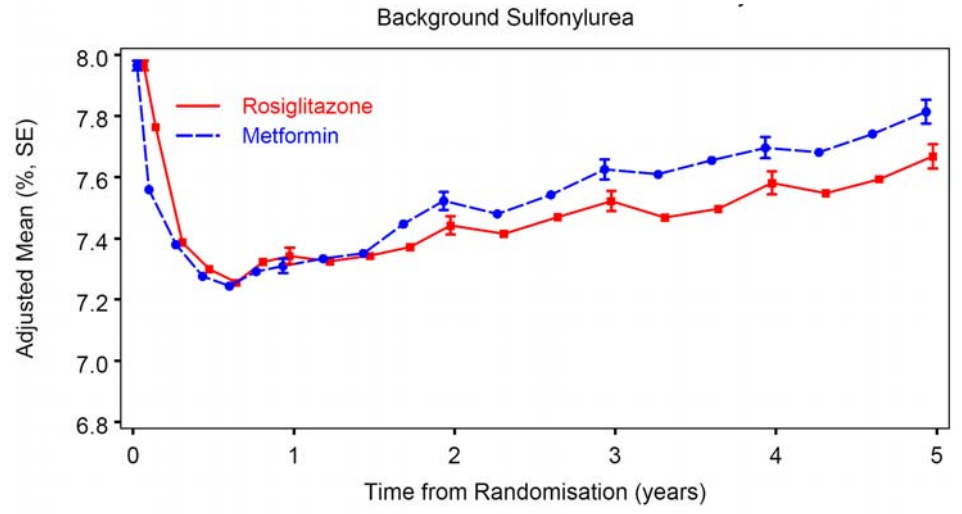
Consistent with the results from ADOPT, the RECORD study showed that RSG in combination with either MET or SU provides long-term glycemic control. For subjects on background MET, the addition of RSG resulted in significantly lower HbA1c at 5 years compared to the addition of SU (Figure 2). For subjects on background SU, the addition of RSG resulted in significantly lower HbA1c at 5 years compared to the addition of MET (Figure 3).

Figure 2 **RECORD: Model-adjusted Mean HbA1c Over Time: Randomized Dual Combination Treatment on Background MET (ITT population)**



Number of Subjects						
Rosiglitazone	1096	965	866	772	695	605
Sulfonylurea	1079	1027	941	869	775	666

Figure 3 **RECORD: Model-adjusted Mean HbA1c over Time: Randomized Dual Combination Treatment on Background SU (ITT population)**



Number of Subjects						
Rosiglitazone	1073	927	804	726	648	560
Metformin	1079	994	910	833	755	652

There is a wealth of long-term data demonstrating durable glycemic control with RSG encompassing 15,803 pt-years. Comparable long-term data are not available for PIO, DPPIVs, or GLP-1s. ADOPT and RECORD have demonstrated that RSG has more durable glycemic control than MET or SU when used as either monotherapy or in combination therapy over the long-term, consistent with RSG's improvement in insulin resistance and beta cell function. This durable glycemic control of up to 5 years

demonstrated with RSG has the potential to reduce and prevent microvascular complications.

2.3. Rosiglitazone Effects on Albuminuria, Microvascular Complications, and Amputations

2.3.1. Albuminuria

The UKPDS and DCCT studies have clearly shown that long-term tight glycemic control significantly improves urinary albumin excretion and reduces progression to nephropathy [UKPDS 33, 1998, DCCT, 1993]. Microalbuminuria is a relatively common complication of diabetes mellitus, affecting between 15% and 60% of subjects with T2DM. Urinary albumin excretion rate between 30 mg/day (considered the upper limit of the normal range) and 300 mg/day define the presence of microalbuminuria. Urinary albumin creatinine ratio (ACR) is often substituted for direct measurement of microalbuminuria in clinical trials due to the simplicity of sample collection.

In three short-term studies that measured ACR, there was a reproducible and consistent decrease from baseline in ACR for RSG-treated subjects with T2DM [Bakris, 2003; Lebovitz, 2001; Bakris, 2006] as would be expected in response to glucose lowering. A decrease from baseline in ACR was further demonstrated in the long-term studies ADOPT and RECORD:

- in the ADOPT study, the mean change in ACR from baseline with RSG was not significantly different from glyburide/glibenclemide (GLY), but was significantly lower compared to MET (Figure 4).
- in the RECORD study with patients treated for an average of 5.5 years, the ACR decreased with RSG treatment in both the background MET and SU strata over the first 2 years and slowly increased thereafter. Urinary ACR was consistently lower in the RSG groups than in the comparator groups (Figure 5).

Figure 4 **ADOPT: Multivariate Linear Model Analysis of Change in Urine Albumin/Creatinine Ratio (Microg/mg) from Baseline to 48 Months (ITT Population, All On-Therapy Data)**

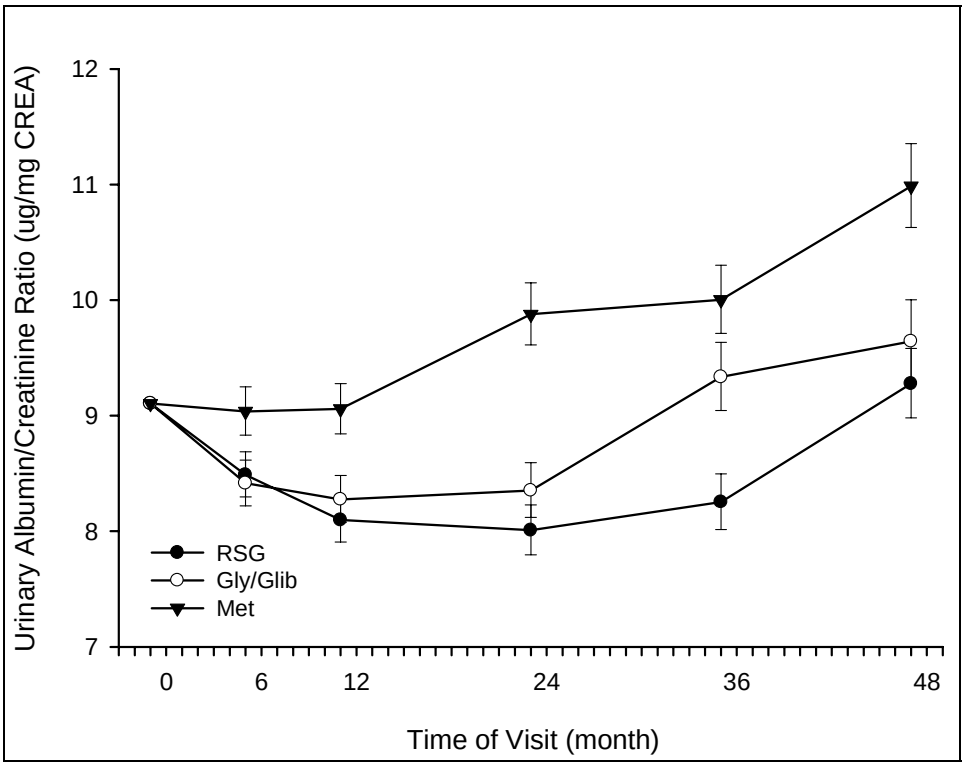
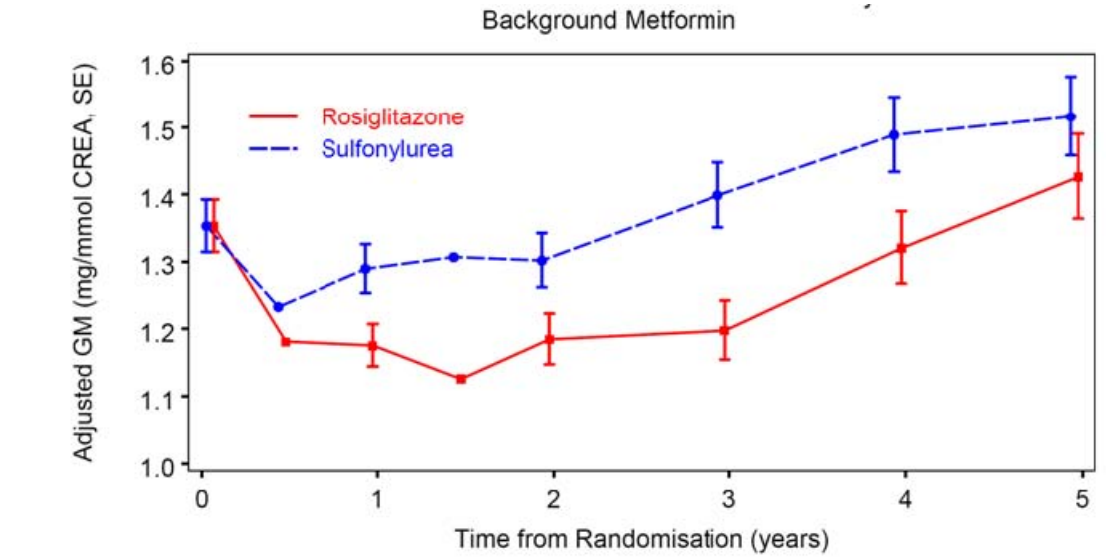
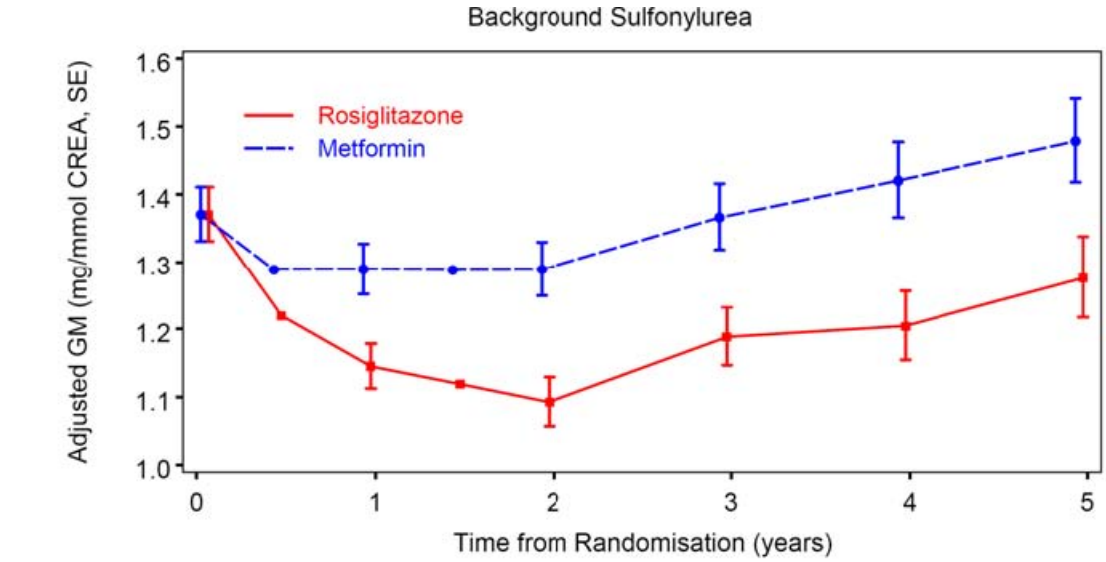


Figure 5 **RECORD: Mean Urinary Albumin:Creatinine Ratio Over 5 years of Treatment**



Number of Subjects						
Rosiglitazone	899	803	724	627	571	503
Sulfonylurea	921	863	791	726	649	562



Number of Subjects						
Rosiglitazone	891	765	685	606	545	472
Metformin	901	830	770	694	631	542

These long-term reductions in microalbuminuria are consistent with the long-term glycemic improvements demonstrated by RSG.

2.3.2. Microvascular Events

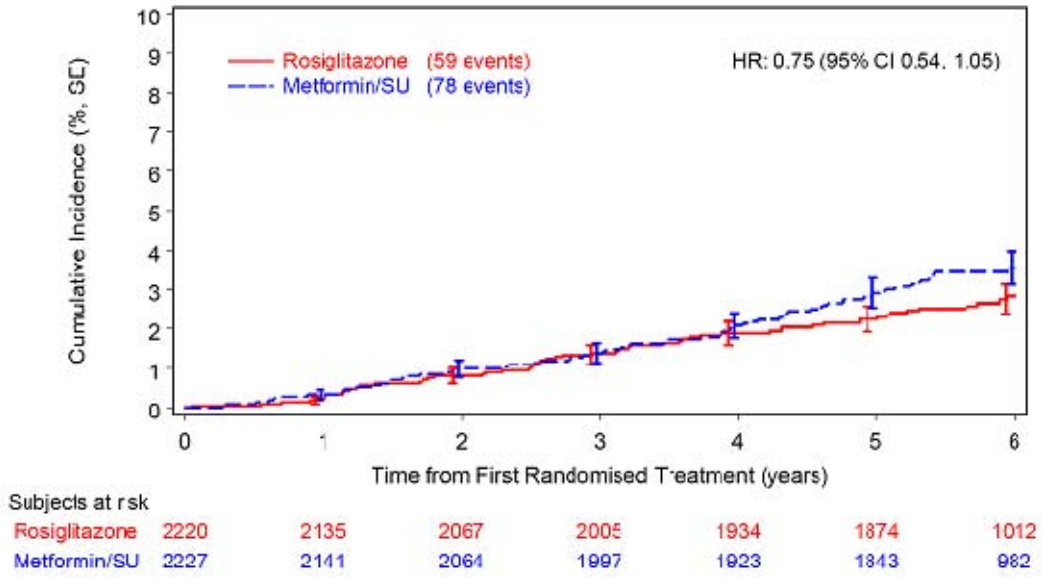
The impact of improvements in glycemic control on microvascular complications can only be assessed in long-term clinical studies. The UKPDS study demonstrated reductions in microvascular complications in those patients who achieved improvements in glycemic control with MET or SU [UKPDS 33, 1998]. In RECORD there was the opportunity to determine the comparative profile of RSG to MET or SU on the occurrence of microvascular complications. The time to first occurrence of any microvascular event (diabetes-related, including eye and foot events) did not differ significantly between the RSG and MET/SU groups (Table 1 and Figure 6). No renal microvascular events (defined as end stage renal events) were reported.

Table 1 RECORD: Occurrence of Microvascular Events (ITT population)

Time to first occurrence of microvascular events	Treatment Group	
	RSG (N=2220)	MET/SU (N=2227)
No. (%) of subjects with any microvascular event [no. of events]	59 (2.7) [75]	78 (3.5) [105]
Incidence: rate/100 PY (95% CI)	0.48 (0.37- 0.63)	0.65 (0.51- 0.81)
Hazard ratio[a], (95% CI); p-value	0.75 (0.54- 1.05); p=0.0969	
Absolute rate difference/100 PY	-0.16 (-0.35- 0.03)	
No (%) of subjects with an eye[b] event [no. of events]	42 (1.9) [53]	52 (2.3) [65]
Incidence: rate/100 PY (95% CI)	0.34 (0.25- 0.47)	0.43 (0.32- 0.56)
Hazard ratio[a] , (95% CI); p-value	0.81 (0.54-1.21); p=0.2980	
Absolute rate difference/100 PY	-0.08 (-0.24-0.07)	
No (%) of subjects with new therapeutic intervention (laser coagulation carried out for the first time) for the treatment of diabetic retinopathy[c] [no. of events]	12 (0.5) [16]	21 (0.9%) [24]
No (%) of subjects with cataract extraction[c] [no. of events]	29 (1.3) [36]	33 (1.5) [40]
No (%) of subjects with new blindness (on one eye) [c] [no. of events]	1 (<0.1) [1]	1 (<0.1) [1]
No (%) of subjects with any foot event[d] [no. of events]	19 (0.9) [22]	28 (1.3) [40]
Incidence: rate/100 PY (95% CI)	0.15 (0.09-0.24)	0.23 (0.15-0.33)
Hazard ratio[a] , (95% CI); p-value	0.67 (0.37-1.20); p=0.1783	
Absolute rate difference/100PY	-0.07 (-0.18-0.03)	

a. Based on Stratified (by background stratum) Cox's Proportional Hazards Model: Time=Treatment. HR is relative to MET/SU.
b. New therapeutic intervention (laser coagulation carried out for the first time) for the treatment of diabetic retinopathy, cataract extraction, new blindness (on one eye)
c. Subjects may have more than one type of event
d. New foot ulcer

Figure 6 RECORD: Cumulative Incidence of Time to First Occurrence of Any Microvascular (Diabetes-related) Event (ITT population)



The data from RECORD show that the microvascular events with RSG are not greater than those reported with MET and SU. Reductions in microvascular events have been shown with MET and SU in the [UKPDS 33, 1998] study.

2.3.3. Amputations

In diabetic patients there is an increased risk of amputations due to peripheral vascular disease, neuropathy, and an increased risk of infections. The impact of treatment on amputations requires data from long-term clinical studies, e.g. RECORD, where data greater than 5 years are available. In RECORD, there were fewer amputations with RSG (6) as compared with the combination of MET and SU (23).

2.4. Overall Conclusions on Glycemic Control and Microvascular Effects

Rosiglitazone has been extensively studied in the short-term and has demonstrated glycemic efficacy with up to 1.5% reduction in HbA1c. In addition, there is a wealth of long-term glycemic data showing durable glycemic control compared to MET and SU. Short- and long-term reductions in microalbuminuria have been demonstrated with RSG treatment. Importantly, the availability of long-term studies on RSG has allowed an evaluation of its impact on microvascular complications. There are limited or no published long-term microvascular data for PIO, DDPIVs, and GLP-1s, thus comparison with the established profile with RSG is difficult. In RECORD, there was no increase in microvascular complications compared to MET and SU, agents that have demonstrated reductions in microvascular events in the UKPDS 33 study. Moreover in the RECORD study, there were fewer amputations with RSG compared to MET and SU.

2.5. Rosiglitazone Effects on Macrovascular Risk Factors

Patients with T2DM are at a 2-4 fold increased risk of macrovascular complications compared to non diabetic subjects; this increased risk is partly due to obesity, dyslipidemia, and hypertension as well as hyperglycemia. It is important to have a multifactorial approach to the treatment of these patients. Therefore diabetes treatment guidelines address the need for treatments to manage these risk factors independent of glycemic control.

2.5.1. Effects on Lipids

LDL cholesterol is associated with increased cardiovascular disease, and it is important to manage this risk factor and other lipid abnormalities in T2DM. The ADA and NICE Guidelines recommend that statin therapy should be added for diabetic patients over the age of 40 regardless of lipid levels [ADA, 2010, Royal College of Physicians, 2008].

Trials that included patients with diabetes and coronary heart disease have shown that cholesterol lowering with statins substantially reduced the risk of subsequent cardiovascular events. Furthermore, in primary prevention studies such as the CARDS study [Calhoun, 2005] benefit was seen with atorvastatin even in patients without a high LDL cholesterol and these results support the use of statins in the majority of patients with type 2 diabetes.

Changes in lipids have been evaluated during the clinical development program for RSG and the short-term lipid effects of RSG have been well described when used as monotherapy or in combination with other anti-glycemic agents [Malinowski, 2000; Wagstaff, 2002]. In 26-week, placebo-controlled studies utilizing 4 mg and 8 mg of RSG, treatment with RSG was associated with:

- a 14.1% to 18.6% increase in low density lipoprotein-cholesterol (LDL-c) level; the increases in LDL-c are associated with a shift in particle size toward the more buoyant and less atherogenic LDL particles
- a 11.4% to 14.2% increase in high density lipoprotein-cholesterol (HDL-c) level
- no difference in LDL-c/HDL-c ratio at one year
- changes in triglycerides have been less consistent and not significantly different from controls.

In the long-term ADOPT study of RSG in T2DM patients where use of statins with appropriate individualization of dosage was encouraged, the LDL-c concentration was lower at 48 months than at baseline in all treatment groups. Although the LDL-c level was significantly higher in the RSG group than the MET and GLY groups by about 8% and 5% respectively, there was no clinically significant difference between RSG, GLY and MET treatment groups in LDL-c:HDL-c ratio at the end of the study. There were no clinically significant changes in triglycerides in any of the treatment groups.

In the RECORD study, statin use was recommended according to local guidelines. There was a higher proportion of RSG patients on statins compared to MET/SU (51% vs 43%

in patients completing 5 years). At 5 years, LDL-c, HDL-c, and Total Cholesterol remained higher in the RSG group compared to MET and SU (Table 2).

Table 2 RECORD: Absolute Change from Baseline to Month 60 in Total, HDL, and LDL Cholesterol

Lipid Parameter		Background Metformin		Background Sulfonylurea	
		Rosiglitazone	Sulfonylurea	Rosiglitazone	Metformin
Total Cholesterol (mmol/L)	Baseline	5.41 (1.06)	5.36 (1.04)	5.57 (1.09)	5.56 (1.09)
	Month 60	5.13 (1.20)	4.90 (1.03)	5.38 (1.39)	5.01 (1.11)
	Change from Baseline	-0.29 (1.21)	-0.48 (1.03)	-0.12 (1.32)	-0.51 (1.18)
HDL-Chlolesterol (mmol/L)	Baseline	1.20 (0.29)	1.19 (0.28)	1.19 (0.29)	1.21 (0.31)
	Month 60	1.35 (0.34)	1.27 (0.32)	1.30 (0.33)	1.29 (0.31)
	Change from Baseline	0.13 (0.24)	0.04 (0.19)	0.11 (0.24)	0.08 (0.23)
LDL-Chlolesterol (mmol/L)	Baseline	3.21 (0.91)	3.15 (0.88)	3.40 (0.89)	3.41 (0.93)
	Month 60	2.88 (1.05)	2.68 (0.89)	3.14 (1.16)	2.86 (0.98)
	Change from Baseline	-0.35 (1.05)	-0.51 (0.88)	-0.20 (1.05)	-0.54 (0.98)
Triglycerides (mmoml/L)	Baseline	2.29 (1.22)	2.37 (1.50)	2.28 (1.74)	2.22 (1.62)
	Month 60	2.05 (1.20)	2.20 (1.50)	2.05 (1.35)	2.01 (1.16)
	Change from Baseline	-0.21 (1.27)	-0.03 (1.32)	-0.21 (1.77)	-0.12 (1.35)

Mean (SD)

Because diabetics should be treated with lipid-lowering therapy as part of standard of care, the effect of statin use in patients treated with RSG has been evaluated in specific studies. [Freed, 2002] assessed the addition of atorvastatin in patients treated with RSG and found that the expected reductions in LDL-c with atorvastatin was maintained. In another study that evaluated the addition of simvastatin to TZD therapy, patients' lipid profiles improved regardless of which TZD was taken. There was no significant difference in mean percentage change in LDL-c between RSG and PIO following the addition of simvastatin [Lewin, 2004].

2.5.2. Effects on Blood Pressure

Patients with T2DM are at increased risk for developing hypertension, and it is recognized that even modest increases in blood pressure (BP) may contribute to overall CV risk. Blood pressure control, as with lipid control, has clearly been shown to be important in reducing CV events [(UKPDS 38, 1998]. As such, the ADA guidelines recommend aiming for BP <130/80 mm Hg [ADA, 2010].

Across the clinical trial program, consistent reductions in blood pressure, low in magnitude (2-3mm Hg), have been observed with RSG therapy. These decreases in BP have been observed in those RSG studies in which ambulatory blood pressure monitoring (ABPM) has been used [Barnett, 2003; Natali, 2004; Negro, 2005; Raji, 2003; Sarafidis, 2004; St John, 2002; Komajda, 2008]. RSG has been shown to reproducibly decrease blood pressure, alone or in combination with MET or SU. PIO has been shown to produce similar blood pressure reductions. Reductions in blood pressure have not been

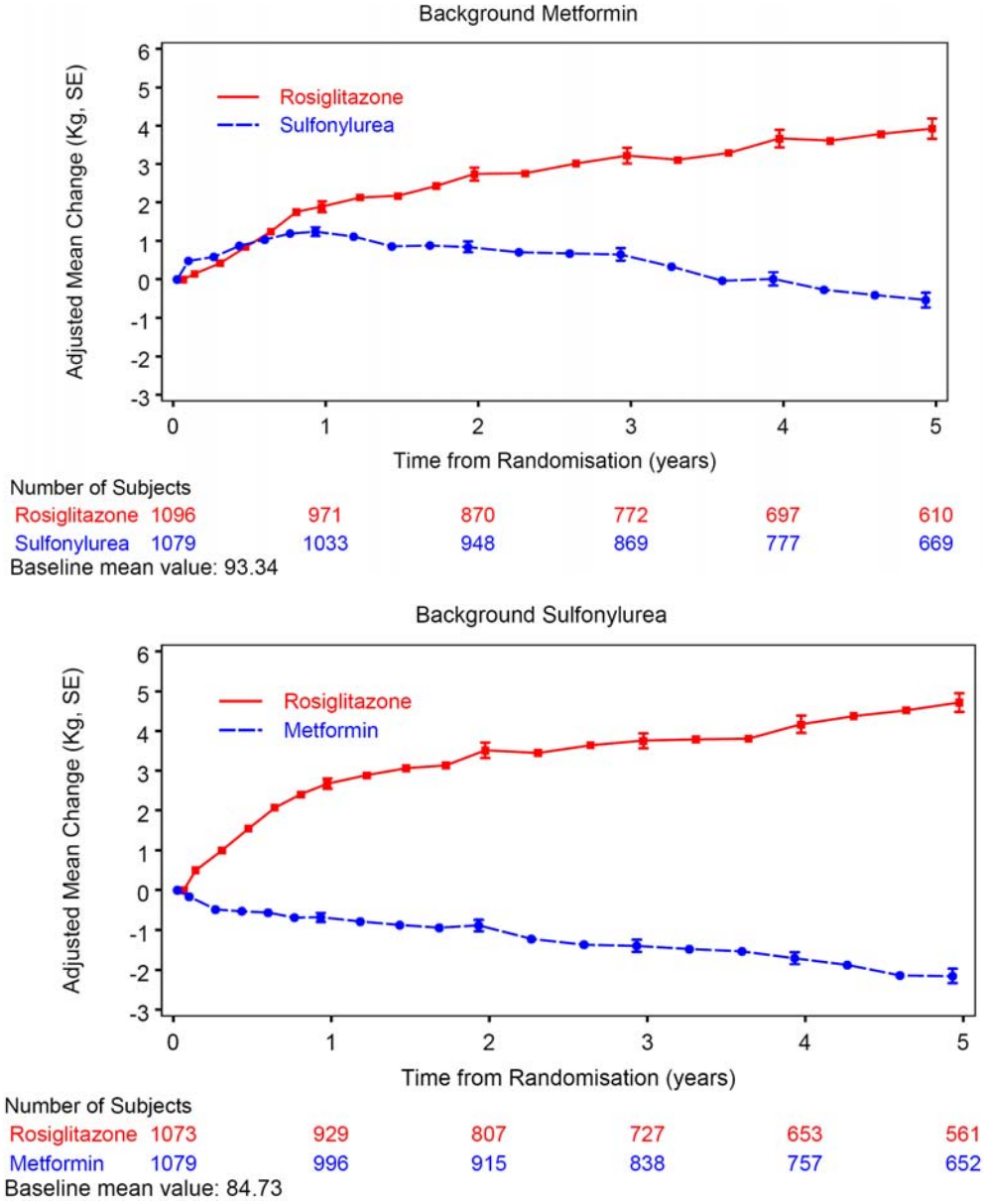
seen with other anti-hyperglycemic agents. In general, reductions in blood pressure in diabetics are associated with reduction in risk of stroke [Stratton, 2006].

2.5.3. Effects on Weight and Visceral Fat

Managing weight in diabetic patients is important. In UKPDS, intensive glycemic control with SU and insulin was associated with an increase in weight, up to 4kg [UKPDS 33, 1998]. Dose-related weight gain is associated with TZD use and probably involves a combination of fluid retention and fat accumulation.

In RECORD, mean body weight increased over time with RSG treatment in both the background MET and background SU strata. In the SU (background MET) group there was a slight increase in weight over the first year followed by a slight decrease over the remainder of the study. In the MET (background SU) group weight decreased slightly over the course of the study (Figure 7).

Figure 7 RECORD: Model-adjusted Mean Body Weight over Time: Randomised Dual Combination Treatment (ITT population)



There is growing evidence that abdominal fat has a stronger relationship with insulin resistance than peripheral, non-abdominal fat [Lefebvre, 1998]. In addition, intra-abdominal (visceral) fat accumulation is associated with a significant increase in overall morbidity and mortality [Bjontorp, 1991; Emery, 1993]. Treatment of patients with T2DM with RSG results in an increase in subcutaneous fat volume, predominantly in non-abdominal sites, but no increase in intra-abdominal fat and a large reduction in hepatic fat [Carey, 2002; Tiikkainen, 2004; Virtanen, 2003].

2.5.4. Overall Conclusion on Macrovascular Risk Factors

Several anti-hyperglycemic agents affect macrovascular risk factors in different ways. SU and insulin are associated with weight gain. Both TZD agents have also been shown to cause weight gain, but also to lower blood pressure. Differences in lipid profiles have been seen in short-term studies but with the addition of a statin,a guideline recommendation, patients' lipid profiles improved regardless of which TZD was taken. In order to establish the impact of changes in these different risk factors on overall CV risk, it is necessary to examine the impact of treatment on both established surrogates and outcome studies.

2.6. Effect of Rosiglitazone on Surrogates of CV Outcomes

Cardiovascular disease is related to atherosclerosis and atherosclerosis progression is correlated with increased risk of coronary events [Ricciardi, 2003; von Birgelen , 2004]. The atherosclerotic process can be assessed non-invasively by measuring the intimal-medial thickness of the carotid arterial wall (cIMT), a potential surrogate of CV outcomes. In addition, atherosclerosis can be directly assessed with the use of intravascular ultrasonography (IVUS).

Treatment with RSG has been shown to slow the progression of carotid atherosclerosis, as measured by changes in carotid intimal-media thickness (cIMT). In a double-blind, randomized controlled study of subjects with insulin resistance, the progression cIMT was significantly reduced (mean change: -0.005 mm vs. 0.021 mm, p=0.007) in the common carotid artery in the diabetic group [Hedblad, 2007]. This observation was confirmed in a second study in diabetic patients randomized to receive either RSG or MET with both mean and maximal cIMT measurements from the common carotid artery [Stocker, 2007]. The effects of RSG on cIMT progression are in general consistent although less definitive in patients without diabetes [Sidhu, 2004; Bhatt 2007]. The largest cIMT assessment in non-diabetic subjects came from STARR (Study of Atherosclerosis with Ramipril and RSG), a cIMT substudy of the DREAM trial, where cIMT was evaluated in more than 1400 subjects at risk for developing diabetes for an average follow up duration of 3 years [Lonn, 2009]. In this STARR study, RSG treatment resulted in a significant reduction of cIMT progression in the common carotid artery.

Two randomized clinical trials (APPROACH and VICTORY) used IVUS as their primary endpoint in assessing changes in atherosclerosis plaque volume.

APPROACH was a double-blind randomized clinical trial comparing the effects of RSG, an insulin sensitizer, and glipizide (GLIP), an insulin secretagogue, on the progression of coronary artherosclerosis [Gerstein, 2010]. Patients with T2DM and coronary artery disease undergoing clinically indicated/planned coronary angiography or percutaneous coronary intervention were randomized to receive RSG or GLIP for 18 months.

RSG reduced atherosclerotic plaque volume compared to GLIP, however, the difference between groups for the main study endpoint did not reach statistical significance (non-significant reduction in the primary endpoint of percent atheroma volume compared to GLIP [–0.21% vs. +0.43%, p=0.12]). RSG significantly decreased normalized total

atheroma volume (-3.9 mm^3 vs. +1.2 mm^3, p=0.04) and was associated with reduced atheroma volume in the most diseased 10mm segment (-5.3 mm^3 vs. -3.6 mm^3, p=0.13) although the difference between groups for this measure did not reach statistical significance. Results of these secondary endpoints are directionally consistent with the primary endpoint, showing no adverse effect of RSG on progression of coronary atherosclerosis.

VICTORY was a double-blind, prospective multi-center randomized placebo-controlled trial to assess the effects of RSG on the prevention of atherosclerosis progression in saphenous vein grafts (SVG) of diabetic patients who had previously undergone coronary artery bypass graft (CABG) surgery. In this 12 month study, in addition to their standard drug therapy, patients were assigned to RSG (up to 8 mg/day or to maximum tolerated dose) or placebo.

RSG did not have a statistically significant impact on atherosclerosis progression in vein grafts despite several favourable cardiometabolic effects compared to standard therapy. Atherosclerosis progression was greater in the placebo arm (increase after 12 months [mm^3=+10 compared to mm^3=+3 with RSG]) although the changes from baseline were small in both arms, and the difference between them was not statistically significant [Bertrand, 2008].

The effect of RSG on surrogates of CV outcomes has been assessed using both IMT and IVUS. None of these trials have demonstrated that RSG is associated with progression of atheroma. Progression of atheroma would be expected to occur in patients with T2DM in the absence of therapies aimed at reducing this progression. Similar studies with PIO have also shown no progression of atheroma. There are limited data on the progression of atheroma with other anti-hyperglycemic agents.

2.7. Safety of Rosiglitazone

RSG has been extensively studied both pre-approval and in the 10 years since initial marketing. The association of RSG with fluid retention and congestive heart failure (TZD class effects) was well characterized from short-term studies. Another TZD class effect, increased risk of fracture, became apparent in long-term studies. Furthermore, concerns were initially raised about the potential for carcinogenic effects of TZDs. Long-term studies of RSG provide strong evidence that it does not pose a carcinogenic risk in humans.

2.7.1. Fluid Retention and Congestive Heart Failure

TZDs, alone or in combination with other anti-hyperglycemic agents, can cause fluid retention which in susceptible subjects can exacerbate and or precipitate congestive heart failure (CHF).

GSK has conducted a number of preclinical and clinical studies to investigate the cause of fluid retention. RSG has been shown to cause sodium retention by both distal and proximal tubular mechanisms. A randomized comparative study in humans which included four diuretics with different sites of action showed that spironolactone was the most effective [Karralliedde, 2006], which favours a predominant role of the ENaC

transporter in the distal tubule, but hydrochlorothiazide, although less active also had a material diuretic effect that is consistent with a proximal tubular action.

The fluid retention results in an increase in plasma volume and in a dose dependent manner can cause edema, and signs and symptoms of congestive heart failure. In the clinical trial program the incidence of CHF events ranged from 0.12% to 2.42% in the RSG group and 0.25% to 1.36% in the control group. The dual combination therapies with the highest incidence is RSG added to established SU and RSG added to established insulin therapy. In RECORD, the incidence of CHF was significantly higher in subjects randomized to RSG compared to active control (61 vs 29) with a HR of 2.10 (95% CI 1.35-3.27), with a difference in absolute incidence of 2.6 CHF events per 1000 patient-years.

In a 52-week, double-blind placebo-controlled echocardiographic study in T2DM patients with established New York Heart Association (NYHA) Class I or II heart failure, RSG in addition to background anti-hyperglycemic medications did not adversely affect left ventricular ejection fraction (LVEF), left ventricular volumes, cardiac index, or transmitral Doppler flow parameters as determined by ECHO [Dargie, 2007]. However, there was a higher incidence of fluid-related end points during treatment with RSG. Most of the fluid-related events did not lead to early withdrawal of patients from the study. The majority of events were managed in the clinic by the timely and appropriate use of diuretics. Increases in CHF medication occurred in 21 (19%) of RSG treated patients compared to 20 (18%) of placebo treated patients with worsening of CHF in 7 (6%) of RSG treated patients compared to 4 (4%) on placebo.

Both TZDs cause fluid retention and can worsen CHF. This adverse effect is highlighted in the label of both products in the US prescribing information in a boxed WARNING. Prescribers are advised to observe patients carefully for signs and symptoms of heart failure, and if signs and symptoms develop to manage the heart failure according to current standards of care and to consider discontinuation or dose reduction. TZDs are not recommended in patients with symptomatic heart failure.

2.7.2. Fractures

In the short-term studies there was no evidence of an increase in the risk of fracture. An increase in the incidence of fracture, particularly in women, only became apparent in the long-term ADOPT study and subsequently was observed in RECORD [Kahn, 2006; Kahn, 2008; Home, 2009]. Over the 4-to 6-year period of ADOPT, the incidence of bone fractures in females was 9.3% (60/645) for RSG versus 3.5% (21/605) for glyburide and 5.1% (30/590) for MET. The majority of fractures observed in female patients who received RSG were predominantly in the upper arm (humerus), hand, or foot, sites of fracture different from those typically associated with post menopausal osteoporosis (e.g., hip or spine). An increase in fractures in female patients receiving long-term treatment with PIO has also been reported. Information about the risk of fractures is contained in the WARNINGS and PRECAUTIONS section of the US Prescribing Information for both TZDs.

2.7.3. Carcinogenicity

ADOPT and RECORD provide long-term exposure data to assess carcinogenicity risk. ADOPT provides 4954 patient-years experience on RSG, 4244 on GLY and 4906 on MET and a median follow-up of 4.0 years. The percentage of subjects with malignant neoplasms or cancers on therapy was low and similar between the RSG group (68 subjects, 4.7%, 1.4/100 PY) and the other two groups (79 subjects, 5.5% for GLY/GLIB, 1.9/100 PY and 84 subjects, 5.8%, 1.7/100 PY for MET), respectively. RECORD provides 10,848 patient years exposure on RSG in combination with MET and/or SU and 10, 209 patient years exposure on the combination of MET and SU. The rate of neoplasms or cancer was similar across the 2 groups (248 subjects, 11.2%, 2.43/100 PY for RSG in dual or triple combination with MET/SU; 259 subjects, 11.6%, 2.70/100 PY for MET/SU). These long-term data indicate that RSG does not pose a carcinogenic risk in humans.

Comparable long-term data assessing the carcinogenicity risk with other anti-glycemic agents, including PIO, DDPIVs, and GLP-1s are not currently available.

3. REVIEW OF GSK INTEGRATED CLINCIAL TRIAL ANALYSES AND OBSERVATIONAL STUDIES

There have been multiple meta-analyses of RSG studies that have been published utilizing different numbers of studies or different methodologies. This summary focuses on the meta-analyses conducted by GSK (integrated clinical trials, ICTs) since the analyses were conducted according to a prospective analysis plan using patient-level data from randomized, double-blind, controlled trials in T2DM patients.

A number of observational studies have been conducted to evaluate the occurrence of major cardiovascular events during treatment with a thiazolidinedione (TZD) (RSG or pioglitazone [PIO]) These studies apply epidemiologic research utilizing real-world drug use data. GSK has comprehensively reviewed the literature on observational cardiovascular studies in which RSG was studied and that have been published since July 2007.

3.1. Integrated Clinical Trial Analyses

In January 2004, the World Health Organization's (WHO) Uppsala Drug Monitoring Center published a notification of a review of post-marketing safety reports on "Thiazolidinediones and cardiac disease" in the WHO newsletter SIGNAL. In the absence of long-term data at that time, GSK deemed it important to undertake an exploratory patient-level meta-analysis of RSG studies to gain additional perspective on the current database for events of heart failure and myocardial ischemia. This effort was undertaken with full recognition of the important limitations that impact the interpretation of any meta-analysis across studies that were not designed to specifically assess the event of interest. At that time, 37 double-blind randomized controlled trials were available that met the criteria for inclusion in the meta-analysis. Subsequently, the integrated clinical trial analysis has been updated twice by GSK (ICT-42 and ICT-52) with new studies that met the original criteria for inclusion in the meta-analyses.

Criteria for inclusion in all three ICTs were:

- GSK- sponsored study
- Studies must have included a control regimen (either placebo or active).
- Study populations must have been adults who had T2DM.
- Studies must have included data on either 4 mg or 8 mg RSG doses.
- Studies must have been double-blind.

To avoid complications of heterogeneity, the long-term studies ADOPT and RECORD were not included in the three ICT analyses.

GSK recognized that there were limitations to the ICT analyses. With the exception of one study (APPROACH), the studies were not designed to systematically collect or assess CV endpoints, nor did they have in-stream blinded adjudication of events. Moreover, the studies had small numbers of events, the studies were of a relatively short-

term duration (≤6months), and the studies were not sufficiently powered to assess cardiovascular outcomes. Because of these limitations, GSK considered the results of the ICT analyses hypothesis generating.

Across the pooled treatment regimens evaluated in the ICT-37, the results of the logistic regression analyses were inconclusive and the 95% confidence intervals were wide and included 1 for all treatment comparisons. Across the pooled treatment regimens evaluated in the ICT-42, which encompassed 14,237 subjects and 258 (172 RSG and 86 Control) myocardial ischemic events, the HR for myocardial ischemic events was 1.30 [(95% CI 1.004-1.685), p=0.047] for RSG versus Control. The results of this ICT-42 and the results of the FDA-conducted analysis of these same studies were discussed at the July 30, 2007, Joint Advisory Committee meeting. The minutes of the meeting captured that most of the committee members agreed that there was at least a strong signal for increased cardiac risk, though concerns were raised about the short duration of the trials; the quality of the data; low number of cardiac events; lack of cardiac event adjudication; and concerns about the heterogeneity of the study population.

In December 2008, the ICT was updated with 10 additional studies, that met the original criteria, with data that became available since the completion of the ICT-42. The ICT-52 focused on myocardial ischemic events and major adverse cardiovascular events (MACE; a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke). The two primary objectives for the ICT-52 were:

- to estimate the myocardial ischemia Hazard Ratio (HR; and associated 95% confidence interval, CI) for RSG relative to control (active or placebo)
- to estimate the MACE HR and associated CI for RSG relative to Control (active or placebo).

One of the 10 additional studies (APPROACH) was conducted in subjects at a higher risk for cardiovascular events and MACE was a pre-defined secondary endpoint prospectively reviewed by a blinded clinical endpoint committee, in contrast to the other 9 studies.

3.1.1. Myocardial Ischemia

The HR and 95% CI for myocardial ischemia in ICT-52 are presented in Table 3. For comparison, the HR and 95% CI of ICT-42 and the 10 additional studies are also presented. The overall incidence of myocardial ischemic events in the ICT-52 was low and similar between RSG (2.21%, 4.34 events per 100 PY) and Control (2.08%, 3.98 events per 100 PY), with no significant difference between groups (HR 1.098 [95% CI 0.890-1.354] p=0.383).

Table 3 Myocardial Ischemia Serious and Non-serious AEs: Results from Proportional Hazards Regression Analysis (All Randomized Subjects)

	Hazard Ratio[1]		RSG		Control	
	HR (95% CI)	p-value	Events/ subjects (%)	PY (Rate 100 PY)	Events/ subjects (%)	PY (Rate 100 PY)
ICT-42	1.300 (1.004-1.685)	0.047	172/8604 (2.00)	4143.3 (4.15)	86/5633 (1.53)	2675.3 (3.21)
10 additional studies	0.822 (0.564-1.198)	0.307	50/1435 (3.48)	977.5 (5.12)	59/1323 (4.46)	963.5 (6.12)
ICT-52	1.098 (0.890-1.354)	0.383	222/10039 (2.21)	5120.8 (4.34)	145/6956 (2.08)	3638.8 (3.98)

1. Comparison is based on pooled RSG treatment group against non-RSG treatment group (Control) without covariates.

3.1.2. MACE

The HR and 95% CI for MACE, and each individual component of MACE, in the ICT-52 are presented in Table 4. For comparison, the HR and 95% CI in ICT-42 and the 10 additional studies are also presented. For the ICT-52, the incidence of MACE was low and similar for RSG (0.80%, 1.56 events per 100 PY) and Control (0.73%, 1.40 events per 100 PY), with no significant difference between groups (HR 1.121 [95% CI 0.789-1.593] p=0.525). There were no significant differences between RSG and Control for any of the individual components of MACE.

Table 4 MACE (and MACE components): Results from Proportional Hazards Regression Analysis (All Randomized Subjects)

	Hazard Ratio[1]		RSG		Control	
	HR (95% CI)	p-value	Events/ subjects (%)	PY (Rate 100 PY)	Events/ Subjects (%)	PY (Rate 100 PY)
ICT-42[1]	1.16 (0.77-1.74)	0.47	63/8604 (0.73)	4143.3 (1.52)	38/5633 (0.67)	2675.3 (1.42)
CV Death	*1.91 (0.79-4.64)*	-	*18/8604 (0.21)*	- *(0.43)*	*7/5633 (0.12)*	- *(0.26)*
MI (SAE)	*1.59 (0.93-2.71)*	-	*45/8604 (0.52)*	- *(1.09)*	*20/5633 (0.36)*	- *(0.75)*
Stroke (SAE)	*0.48 (0.23-0.98)*	-	*13/8604 (0.15)*	- *(0.31)*	*18/5633 (0.32)*	- *(0.67)*
10 additional studies[2]	1.294 (0.628-2.664)	0.485	17/1435 (1.18)	977.5 (1.74)	13/1323 (0.98)	963.5 (1.35)
CV Death	*0.589 (0.141-2.467)*	*0.469*	*3/1435 (0.21)*	- *(0.31)*	*5/1323 (0.38)*	- *(0.52)*
MI (SAE)	*1.233 (0.486-3.124)*	*0.660*	*10/1435 (0.70)*	- *(1.02)*	*8/1323 (0.60)*	- *(0.83)*
Stroke (SAE)	*2.474 (0.480-12.761)*	*0.279*	*5/1435 (0.35)*	- *(0.51)*	*2/1323 (0.15)*	- *(0.21)*
ICT-52[2]	1.121 (0.789-1.593)	0.525	80/10039 (0.80)	5120.8 (1.56)	51/6956 (0.73)	3638.8 (1.40)
CV Death	*1.264 (0.621-2.572)*	*0.518*	*21/10039 (0.21)*	- *(0.41)*	*12/6956 (0.17)*	- *(0.33)*
MI (SAE)	*1.406 (0.891- 2.218)*	*0.143*	*55/10039 (0.55)*	- *(1.07)*	*28/6956 (0.40)*	- *(0.77)*
Stroke (SAE)	*0.630 (0.333-1.191)*	*0.155*	*18/10039 (0.18)*	- *(0.35)*	*20/6956 (0.29)*	- *(0.55)*

1. Comparison is based on stratification for treatment comparison strata with covariate adjustments.
2. Comparison is based on pooled RSG treatment group against non-RSG treatment group without covariates.

SAE=Serious Adverse Events

3.1.3. Conclusions

Across the pooled treatment regimens evaluated in the ICT-42, which encompassed 14,237 subjects and 258 (172 RSG and 86 Control) myocardial ischemic events, the HR for myocardial ischemic events was significant for RSG vs control [1.300 (95% CI 1.004-1.685), p=0.047]. With the addition of 10 studies encompassing 2,758 additional subjects with 109 (50 RSG and 59 Control) more myocardial ischemic events, a HR of 1.098 (95% CI 0.890-1.354, p=0.383) was observed for the ICT 52, showing no significant difference from between RSG and control. The change in the hazard ratio based on a relatively small difference between the ICT 42 and 52 study datasets indicates the fragility of any of the hazard ratios determined using this methodology, particularly when the event rate is low and the confidence intervals are relatively wide.

3.2. Observational Studies

In this section, the observational studies that have been published since 2007 are summarized. Twenty-one such studies were identified that constitute a much larger dataset than the dataset available in 2007, which did not show an increase in CV risk with

RSG. Of the twenty-one new studies, one was a cross-sectional study, six were nested case-control studies, and 14 were retrospective cohort studies. The cross sectional study did not provide estimates of relative risk; therefore it was not included in the summary of findings of these studies discussed below. A summary of each study including its study design and results is located in Appendix 3.

Each of these studies was a retrospective assessment of information on patients in large healthcare databases from various healthcare systems. These studies were conducted in the United States (US), Canada, Taiwan, and the United Kingdom (UK). The cardiovascular outcomes assessed varied among the studies. The majority of studies (n=17) assessed myocardial infarction as an outcome. Some studies assessed congestive heart failure (n=9), coronary revascularization (n=3), coronary artery disease (n=2), cardiovascular death (n=2), serious atherosclerotic cardiovascular disease (n=1), and myocardial infarction combined with stroke (n=1). The studies varied in size and duration of follow-up as well as in the adjustment for confounders. Some studies were better designed (e.g., cohort vs case control) and analysed (e.g., accounted for varying exposure) than others. The studies have been summarized according to the cardiovascular outcomes addressed. Major cardiovascular events were assessed for RSG and PIO in all of these studies, either in a head to head comparison or in comparison to other anti-glycemic agents.

In considering the contribution of results of observational studies to the body of evidence on the cardiovascular safety of RSG, it is important to consider the advantages and limitations of this type of study. Observational studies complement the results of clinical trials in that the data represent drug use in a real world setting. Treatment exposures are based on routine care decisions by the patient's physician rather than being assigned according to a controlled protocol. Moreover, the results may be applied more generally to the population as a whole as they typically provide access to larger and more diverse groups of patients than in a clinical trial setting. Observational studies allow comparisons of outcomes between active comparators. Cohort studies in particular can provide a large amount of patient data over a long period of follow-up and, if unbiased, reflect the "real-life" cause-effect temporal sequence of events [Strom, 2005].

However, as treatment exposures are not assigned in a randomized fashion as in most clinical trials, selection bias may occur given some underlying, and often not recorded, reasons for choice of the medication under study, in this case TZDs. For example, patients receiving TZDs may have failed other anti-glycemic agents, may have more co-morbid conditions at baseline, and more disease progression. Some drug benefit reimbursement criteria for RSG (e.g., the Ontario Drug Benefit) restrict reimbursement to patients who have failed or have contraindications to other diabetes drugs. Therefore patients taking RSG are likely to differ from those not taking RSG in ways that may be associated with cardiovascular outcomes independent of the treatment itself. Importantly, there is usually no adjudication of endpoints in observational studies. Sudden death is not readily captured in claims databases except for individuals who died within a few hours of a precipitating event that led to a hospital admission. In the US, ascertaining death and its cause in claims databases requires linking to the National Death Index. Therefore myocardial infarctions resulting in sudden death are under-ascertained in claims databases. Often there is a lack of information on important cardiovascular risk

factors in claims databases (e.g., smoking, duration of diabetes, glycemic control) as well as lack of information on actual time on treatment. The fundamental difference between randomised trials and observational research is that residual confounding is assumed to be eliminated by randomisation in clinical trials, whereas it may remain in an observational study.

3.2.1. Studies Comparing Myocardial Infarction in Rosiglitazone versus Other Anti-Glycemic Agents

The majority of observational studies assessed myocardial infarction as an outcome. Thirteen studies comparing RSG and other anti-glycemic agents assessed myocardial infarction as an outcome (summarized in Table 15 in Appendix 3 in order of publication date). Some studies compared RSG to various other anti-glycemic agents combined whereas others made specific comparisons to MET and/or SU

Comparison to other anti-glycemic agents combined: Nine [Lipscombe, 2007; McAfee, 2007; Koro, 2008; Walker , 2008; Dore, 2009; Habib, 2009; Ramirez, 2009; Stockl, 2009; Vanasse, 2009] of the thirteen studies compared RSG to various other anti-glycemic agents combined. Studies by Koro, McAfee, and Walker were GSK-sponsored studies. The results from six of the studies [McAfee, 2007; Koro, 2008, Walker, 2008; Dore, 2009; Habib, 2009; Stockl, 2009] indicated no statistically significant difference in the risk of myocardial infarction between RSG and other anti-glycemic agents, while three studies [Lipscombe, 2007; Ramirez, 2009; Vanasse, 2009] showed a statistically significant increased risk of myocardial infarction for RSG compared to other anti-glycemic agents.

Studies with lower variance of estimate and tighter confidence intervals [e.g., Koro, 2008; Walker, 2008 and Stockl, 2009] have risk ratios that are very close to one, indicating no difference in the risk of myocardial infarction between RSG and other anti-glycemic agents (Appendix 3, Figure 19). One study [Vanasse, 2009] with low variance indicated a statistically significant increased risk for myocardial infarction associated with RSG. Vanasse reported an increased risk of myocardial infarction with RSG but no increased risk of cardiovascular mortality or all cause mortality.

Studies conducted by [Ramirez, 2009 and Lipscombe, 2007] have wide confidence intervals reflecting low precision of the risk ratio estimates.

Comparison to Sulfonylurea: Three studies [Brownstein, 2010; Hsiao, 2009; Dormuth, 2009] compared RSG to sulfonylurea. Two of the three studies showed no statistically significant difference in the risk of myocardial infarction between the treatment groups and one showed a statistically significant increased risk [Brownstein, 2010].

Comparison to Metformin: Two [Brownstein, 2010 and Hsiao, 2009] of the three studies that compared RSG to SU also compared RSG to MET and showed that RSG was associated with a statistically significant higher risk of myocardial infarction compared to MET (Appendix 3, Figure 19). In a third study [Tzoulaki, 2009] that compared RSG to MET, there was no statistically significant difference in the risk of myocardial infarction between the treatments compared. It is worth noting that in addition to the 13 studies presented in Table 15 in Appendix 3, [Margolis, 2008] conducted a sub-analysis of their

study examining serious atherosclerotic vascular disease in which they limited the outcome to clinical diagnosis of myocardial infarction. The study showed that RSG was associated with statistically significant lower risk of serious atherosclerotic vascular disease compared to other anti-glycemic agents. The authors stated that limiting the outcome to myocardial infarction had minimal effect on the point estimates.

3.2.2. Studies Comparing Myocardial Infarction in Rosiglitazone versus Pioglitazone

Eleven studies comparing RSG to PIO assessed myocardial infarction as an outcome (Appendix 3, Table 16). Studies by Koro, Walker, and Ziyadeh were GSK-sponsored studies. Seven of the eleven [Koro, 2008; Walker, 2008; Winkelmayer, 2008; Dormuth, 2009; Habib, 2009; Juurlink, 2009; Stockl, 2009] studies indicated no statistically significant difference between RSG and PIO with respect to the risk of myocardial infarction (Appendix 3, Figure 20). Studies with lower variance of estimate and tighter confidence intervals [e.g., Koro, 2008; Walker, 2008; Winkelmayer, 2008; Juurlink, 2009] have risk ratios that are very close to one, indicating no difference in the risk of myocardial infarction between RSG and PIO.

On the other hand, studies conducted by [Stockl, 2009; Brownstein, 2010 and Hsiao, 2009] have wide confidence intervals reflecting low precision of the risk ratio estimates. Three studies [Gerrits, 2007; Brownstein, 2010; Ziyadeh, 2009] indicated a statistically significant increased risk for myocardial infarction with RSG compared to PIO. It should be noted that two of these three studies [Gerrits, 2007; Ziyadeh, 2009] were derived from the same database. One study [Hsiao, 2009] had varying results depending on the medication-based strata: there was a statistically significant decreased risk for RSG compared to PIO for MET-based therapy; and no difference between RSG and pioglitazone for sulfonylurea-based and sulfonylurea/MET-based therapy. It is also worth noting that in addition to the 11 studies presented in Table 16 in Appendix 3, [Margolis, 2008] conducted a sub-analysis of their study examining serious atherosclerotic vascular disease in which they limited the outcome to clinical diagnosis of myocardial infarction. The study showed no difference in the risk of serious atherosclerotic vascular disease between RSG and PIO. The authors stated that limiting the outcome to myocardial infarction had minimal effect on the point estimates.

3.2.3. Studies Comparing Other Cardiovascular Outcomes (Coronary Artery Disease, CHF, Coronary Revascularization, CV Death and Serious Atherosclerotic Vascular Disease) in Rosiglitazone versus Other Anti-glycemic Agents

Seven studies [Lipscombe, 2007; Habib, 2009; Hsiao, 2009; Pantalone, 2009; Ramirez, 2009; Tzoulaki, 2009; Vanasse, 2009] comparing RSG to other anti-glycemic agents assessed congestive heart failure as an outcome. Two studies [Habib, 2009; Pantalone, 2009] assessed coronary artery disease. Two studies [McAfee, 2007; Walker, 2008] assessed coronary revascularization/myocardial infarction, one study [Margolis, 2008] assessed serious atherosclerotic vascular disease including myocardial infarction, unstable angina, cardiac death, and coronary artery reperfusion procedure including closed (e.g., angioplasty) and open (e.g., coronary artery bypass) procedures, two

[Ramirez, 2009; Vanasse, 2009] assessed cardiovascular death, and one study [Shaya, 2009] assessed myocardial infarction combined with stroke. Studies by McAfee and Walker were GSK-sponsored studies. These studies are included in Appendix 3, Table 17.

Of the studies that assessed congestive heart failure, two studies [Hsiao, 2009; Pantalone, 2009] compared RSG to sulfonylurea and three studies [Hsiao, 2009; Pantalone 2009; Tzoulaki, 2009] compared RSG to MET, specifically, whereas the remaining four [Lipscombe, 2007; Habib, 2009; Ramirez, 2009; Vanasse, 2009] compared RSG to other anti-glycemic agents combined. The studies that compared RSG to SU or MET (with the exception of [Pantalone, 2009]) showed a non-statistically significant increased risk of congestive heart failure in RSG compared to sulfonylurea or MET. The increased risk ranged from 16% to 30%. Results from three [Lipscombe, 2007; Habib, 2009; Vanasse, 2009] of the four studies that compared RSG to other anti-glycemic agents combined showed a statistically significant 65% to 98% increased risk of congestive heart failure associated with RSG. The third study [Ramirez, 2009] showed an increased risk of CHF with RSG, which was not statistically significant.

The two studies [Habib, 2009; Pantalone, 2009] that assessed coronary artery disease or coronary heart disease as an outcome showed no statistically significant difference between RSG and other anti-glycemic agents including sulfonylurea and MET.

Studies [McAfee, 2007; Walker, 2008] that assessed either coronary revascularization or coronary revascularization with or without myocardial infarction showed no statistically significant difference in the risk between RSG and other anti-glycemic agents combined. Results from the study [Margolis, 2008] that assessed serious atherosclerotic vascular disease showed a statistically significant decreased risk associated with RSG compared to other anti-glycemic agents combined. One of the two studies [Ramirez, 2009] that assessed cardiovascular death showed a statistically significant increased risk of CV death associated with RSG compared to other anti-glycemic agents combined. The second study that assessed cardiovascular death [Vanasse, 2009] showed a non-statistically significant decreased risk for RSG compared to other anti-glycemic agents.

One study [Shaya, 2009] assessed the risk of myocardial infarction combined with stroke in RSG users compared to other oral anti-glycemic agent users showed a statistically significant increased risk for RSG users compared to other anti-glycemic agents.

3.2.4. Studies Comparing Other Cardiovascular Outcomes (Coronary Artery Disease, CHF, Coronary Revascularization, CV Death and Serious Atherosclerotic Vascular Disease) in Rosiglitazone versus Pioglitazone

There are five studies that assessed congestive heart failure [Winkelmayer, 2008; Habib, 2009; Hsiao, 2009; Juurlink, 2009; Pantalone, 2009], three studies of coronary revascularization [Walker, 2008; Ziyadeh, 2009] and coronary revascularization with or without myocardial infarction [Gerrits, 2007; Walker,2008; Ziyadeh, 2009], two studies [Habib, 2009; Pantalone, 2009] of coronary artery disease (or coronary heart disease), and one study [Margolis, 2008] of serious atherosclerotic vascular disease (Appendix 3, Table 18). Studies by Walker and Ziyadeh were GSK-sponsored studies.

Of the studies that assessed congestive heart failure, the majority of studies showed an increased risk of congestive heart failure in RSG compared to PIO, and the difference was statistically significant in three [Winkelmayer, 2008; Habib, 2009; Juurlink, 2009] of these studies. Two [Walker, 2008; Ziyadeh, 2009] of the three studies that assessed the risk for coronary revascularization and coronary revascularization, with or without myocardial infarction, showed no statistically significant difference between RSG and PIO. The third study [Gerrits, 2007] showed a statistically significant 15% reduction in the risk of coronary revascularization with or without MI for PIO compared to RSG. For coronary artery (heart) disease, one study [Habib, 2009] showed a statistically significant increased risk and the other study [Pantalone, 2009] showed a non-statistically significant decreased risk for RSG compared to PIO. The retrospective observational study [Margolis, 2008] that assessed the risk of serious atherosclerotic vascular disease showed no statistically significant difference between RSG and PIO.

3.2.5. Discussion and Summary

The observational studies discussed above varied by design, length of time of observation, the duration of diabetes for an individual, the definition of cardiovascular events, the classification of medication exposure, the medications investigated, and the comparisons made.

Since observational studies may be subject to unmeasured biases, inferences from them gain credibility when separate data sources can provide similar answers. In studies comparing RSG to other anti-glycemic agents, six studies showed no statistically significant difference in the risk of myocardial infarction for RSG compared to other anti-glycemic agents while three studies showed a statistically significant increased risk of myocardial infarction for RSG. Studies with lower variance of estimate and tighter confidence intervals all have risk ratios that are very close to one, indicating no difference in the risk of myocardial infarction between rosiglitazone and other anti-glycemic agents.

In studies that directly compared RSG to PIO, as shown in Appendix 3, the majority of studies showed no statistically significant difference in the risk of myocardial infarction between RSG and PIO, others showed PIO to be associated with better outcome compared to RSG and one study had mixed results depending on the medication based strata examined. Studies with lower variance of estimate and tighter confidence intervals have risk ratios that are very close to one, indicating no difference in the risk of myocardial infarction between RSG and PIO. A number of these studies had more RSG than PIO exposed subjects and may therefore be underpowered to detect adverse outcomes in PIO exposed subjects. The more recent comparisons of RSG and PIO may be biased towards better cardiovascular outcomes for PIO due to the recording of more rule-out diagnosis of ischemic events for RSG driven by media attention. The degree of statistical uncertainty arising, even in very large observational studies, means that the data must be interpreted with caution, further supporting the importance of the long-term randomized trial evidence base.

Observational studies are helpful in detecting drug related adverse events that are greatly increased in rate by the drug. They become less useful when the event of interest, in this

case cardiovascular events, is confounded by the disease (diabetes) and when the event rate may be modestly increased by the drug. When it comes to confirming safety signals, experts in the field have argued that epidemiologic data are uncertain in cases when the risk of adverse events is increased 1.5-fold or less. Conventionally, epidemiologists consider an association with a relative risk of less than 2.0 a weak association [Strom, 2005; Shapiro, 2000]. If the relative risk is less than 2.0, it may not be possible to judge whether or not it can be entirely accounted for by bias [Shapiro, 2000]. The vast majority of the relative risk estimates discussed in this briefing document are not as high as 2, so it cannot be ruled out that the observed weak association can be due to bias, further supporting the importance of the long-term randomized trial evidence base.

Observational studies provide drug use data comparing various anti-glycemic agents in a real-world setting but these studies have their limitations as discussed above. Truly long-term follow-up of a stable regimen may not be feasible in unselected outpatient settings in the US. Only direct head-to-head comparisons in prospective randomized-controlled trials, for example the RECORD study, enable widely convincing conclusions about the comparability of RSG and other anti-glycemic agents. Until randomized trials of sufficient duration comparing RSG to PIO are completed, the question of relative safety and benefit will fall to observational research.

4. RECORD: ROSIGLITAZONE EVALUATED FOR CARDIAC OUTCOMES AND REGULATION OF GLYCEMIA IN DIABETES

Since its inception in 2001, the final results of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) study [Home, 2009], Appendix 4 have become increasingly important in light of the suggestion of an increased risk of myocardial ischemic events in analyses of pooled short-term trials of RSG. This included the patient-level ICT 42 analysis by GSK previously submitted to Regulatory Agencies [Cobitz, 2008] and the study-level analysis of 42 studies by independent investigators which included most but not all of the studies in the ICT 42 [Nissen, 2007].

The RECORD study was a post-marketing commitment to the European Medicine Agency (EMEA). The design was reviewed and approved by the Committee for Proprietary Medicinal Products (CPMP, now known as the Committee for Medicinal Products for Human Use [CHMP]) for the EMEA in October 2000. The RECORD study was required by EMEA to provide long-term overall CV safety data on RSG, and hence inform the benefit risk profile of this product. Following a benefit risk evaluation by CHMP, which included review of the final results of the RECORD study, EMA issued positive opinion which was adopted by the EU Commission in May 2010, who granted renewal of the Avandia marketing license in the EU for an additional five years.

The design and conduct of long-term CV outcome studies in diabetes presents several challenges. The progressive nature of the disease resulting from a decline in beta cell function leads to a need for additional therapy over time, ultimately leading to the use of insulin. The requirement for multiple oral medications, and ultimately insulin injections, makes blinding the treatment strategy impractical in a multi-year study. Consequently, several well known CV outcome studies in diabetes, including UKPDS, VADT, and ACCORD were designed as open label studies. Another challenge for long-term trials is the change of medical practice over time. For example, diabetes guidelines have advised more aggressive targets for management of co-morbid risk factors such as lipids and blood pressure. Therefore, in recent clinical trials in diabetes, this has resulted in lower CV event rates than previously expected.

It was known, at the inception of the RECORD trial, that the open label design and conduct of long-term CV outcome studies in diabetes presented several challenges. The RECORD study was both long-term in nature, taking place over a 9 year period, and was conducted at 364 centres with 1645 events sent for adjudication. In common with other large outcome studies, managing and assessing the large volume of resulting data was challenging. Because of these types of challenges GSK took steps at the both the outset and during the study to seek to manage its conduct as effectively as possible. These steps included:

GSK conducted the RECORD study under the auspices of several independent committees and utilized “hard”, objective endpoints. The design, implementation and analysis of the RECORD study were performed under the supervision of an external academic steering committee (SC). The Steering Committee, chaired by Philip Home,

MD, was composed of experienced diabetologists and cardiologists, and an academic statistician. The SC, which was blinded to treatment, had comprehensive responsibility for the study including:

- defined study design and the protocol
- oversaw the conduct of the study and monitored the CV event rate
- provided oversight of analysis plans and endorsed the interim analysis; also ensured that an independent review was conducted of the interim and final results
- was responsible for the content of the publications and choice of journal submission

The overall safety of the study was under the jurisdiction of the DSMB (data safety monitoring board). The DSMB, chaired by Ian Campbell, MD, was composed of experienced diabetologists, cardiologists, and a statistician. In this role the DSMB, as is usual in this type of study, was unblinded to treatment and operated under the guidance of a DSMB Charter that included stopping criteria for the study. The DSMB met on a regular basis to review the safety data and made recommendations for the continuation of the study.

Adjudication of the cardiovascular endpoints was undertaken by an independent Clinical Endpoint Committee (CEC), chaired by Michel Komajda, MD, and consisting of five cardiologists, one diabetologist and one neurologist. This CEC reviewed and adjudicated CV hospitalizations and deaths in a blinded fashion. Events were determined according to pre-specified protocol definitions, as defined by the CEC Charter. All members had experience and expertise in their field of practice, in the conduct of clinical trials, and were not involved as investigators in the RECORD trial. The neurologist reviewed only the potential stroke and transient ischemic attack (TIA) events.

4.1. Study Design

RECORD was designed to evaluate the long-term CV outcomes of RSG in combination with MET or SU in T2DM patients who were inadequately controlled on maximum permitted or maximum tolerated doses of MET or SU. Dual combination with MET or SU reflected the indicated use for RSG in Europe (EU) on approval by EMEA in 2000.

Subjects were recruited from Europe, Australia, and New Zealand. Subjects with T2DM, aged 40-75 years, with HbA1c >7.0% and ≤9.0%, with a body mass index (BMI) > 25.0 kg/m^2 who were inadequately controlled on maximum permitted or maximum tolerated doses of background monotherapy (MET or SU) were eligible for inclusion. Exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major CV event in the previous 3 months, a planned CV intervention, diagnosed heart failure as defined by the New York Heart Association (NYHA) Classification of Congestive Heart Failure (CHF), and subjects receiving medication for the specific treatment of heart failure (β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, nitrates but not diuretics alone), clinically significant hepatic disease, renal impairment and uncontrolled hypertension.

Following a 4-week run-in period, subjects were randomized in a 1:1 ratio to the addition of either RSG or MET/SU to their background oral anti-glycemic therapy (Figure 8). Subjects with T2DM inadequately controlled on background MET were randomized to the addition of RSG or a SU. Subjects inadequately controlled on background SU were randomized to the addition of RSG or MET. There were three specific SUs mandated by the protocol; sites were permitted to use glibenclamide (GLIB), gliclazide (GLIC), or glimepiride (GLIM) as the background SU and as randomized add- on therapy.

Subjects were to be treated to a target $HbA_{1c} \leq 7.0\%$. If the initial dose had been well tolerated, RSG could be increased to a maximum permitted dose of 8 mg/day, while MET, GLIB, GLIC or GLIM could be gradually increased to the maximum permitted dose as specified by country local guidelines and labeling requirements in order to achieve study target of $HbA_{1c} \leq 7.0\%$.

It is known in diabetes studies that due to the progressive nature of the disease, patients would be expected to need additional medication to maintain glycemic control, particularly in a study of long-term duration. Therefore, the protocol specified a treatment algorithm to maintain glycemic control, taking into consideration the labeling of the respective agents used in Europe. Subjects progressing from triple therapy to insulin in the study were required to stop treatment with RSG in line with the European labeling for Avandia (combination of RSG and insulin contraindicated).

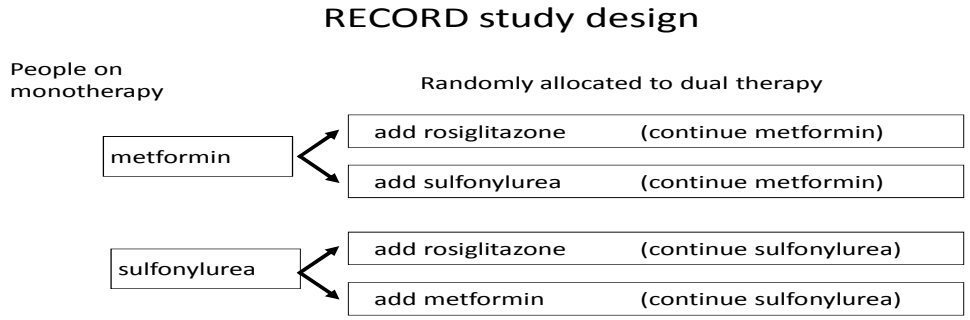
If a subject's HbA1c was ≥8.5% despite having been on a maximum permitted or tolerated dose of add-on study medication for at least 8 weeks and a second HbA1c measurement at least one month later was confirmatory, the subject was to be treated with a third oral glucose lowering therapy (addition of MET or SU in the RSG-treated groups) or switched to insulin alone or in combination with MET and/or SU (control group). In the RSG-treated groups, if HbA1c rose to ≥ 8.5% despite having been on a maximum permitted or tolerated dose of triple oral therapy for at least 8 weeks and a second HbA1c measurement at least one month later was confirmatory, the subject was to be switched to insulin (alone or in combination with MET or SU).

The study was, by necessity, of an open label design, in part as a result of the European label-dictated requirement to withdraw RSG when insulin was introduced. There was no uniform labeling recommendation or common practice for dosing regimen for all the sulfonylureas used in the study (once, twice or three times a day) in the 25 countries in which RECORD was conducted. The recommended dosing frequency for RSG (once or twice a day) does not match that for the higher doses MET in some territories (three times a day). This coupled with the use of three sulfonylureas (glibenclamide, gliclazide, glimepiride) and five formulations (micronized glibenclamide and gliclazide MR used in some countries in place of "conventional" formulations) made blinding unfeasible.

The planned median follow-up was six years. Subjects were followed for CV events throughout the entire study, including when they were in the randomised treatment phase (dual or triple oral therapy for RSG-treated groups and dual oral therapy for MET/SU control groups) and when they moved into the post-randomised treatment phase (subjects switched to insulin in combination with MET and/or SU).

For those patients who withdrew from the study, patients, their carer, or their health care provider were contacted for information if the patient was alive or dead (vital status).

Figure 8 RECORD Study Design Schematic



4.2. Objectives

4.2.1. Primary Objective

The primary objective of this study was to compare the time to first occurrence of CV death or CV hospitalization between those subjects randomized to RSG (RSG group) and randomized to MET/SU (Control group). The primary hypothesis to be tested was non-inferiority of the RSG group versus the control group, defined as an upper limit of the 95% confidence interval (CI) for the hazard ratio (HR) at study end of less than 1.2.

4.2.2. Secondary Objectives

Secondary objectives included a by-stratum comparison (based on background study medication at entry) of glycemic control after 18 months; ambulatory blood pressure monitoring (ABPM) parameters after 6 months and 12 months; and the time to reach the combined CV endpoint of CV death or CV hospitalization over the full duration of the study. The by -stratum comparison consisted of RSG vs SU for background MET and RSG vs MET for background SU.

For the remaining endpoints, comparisons were to be made for RSG group versus control group, and for RSG versus SU for background MET and for RSG versus MET for background SU. The endpoints comprised:

- time to all-cause mortality
- time to first occurrence of definite CHF
- time to first occurrence of all-cause mortality, MI, stroke, definitive CHF and unstable angina

- time to first occurrence of CV death, MI, stroke and unstable angina
- combined CV death and/or CV hospitalization plus microvascular events (diabetes related)
- total number of each of the events in the CV death and/or CV hospitalization endpoint
- total number of microvascular events (diabetes related)
- changes in glycemia and related metabolic parameters
- time to failure of glycemic control on dual combination therapy, defined as an HbA_{1c} ≥8.5%, following at least 8 weeks on maximum tolerated dose of add-on treatment and a confirmatory glycated hemoglobin (HbA_{1c}) ≥8.5% at least 4 weeks later
- time to addition of a third oral therapy for RSG combination groups or switch to insulin for MET and SU combination groups
- time to initiation of treatment with insulin
- general safety through the assessment of changes in physical examinations, vital signs, body weight, clinical laboratory tests, AEs and electrocardiograms (ECG).

An additional composite endpoint was added to the analysis plan at the request of the Steering Committee (CV death, MI, stroke, unstable angina and CHF) and the MACE composite (CV death, acute Myocardial Infarction (MI), stroke) and each individual component (CV death, MI, and stroke) were added by Protocol Amendment 12.

4.3. Demographics

Demographic characteristics and cardiovascular risk factors were well-balanced at baseline between treatment groups within stratum (Table 5). The proportions of men and women were similar and the vast majority of the subjects was white; mean age was 58 years, and mean BMI was 31.5 kg/m^2. Mean Hb_{A1c} was 7.9%, mean FPG was 9.83 mmol/L and mean time since diagnosis of diabetes was 7.1 years.

Although baseline characteristics were well balanced between treatment groups within a stratum, there were some differences between the MET and SU strata. The background SU stratum had lower mean weight and BMI, longer mean duration of diabetes at baseline and higher mean age compared with the background MET stratum. There were a higher percentage of patients with IHD at baseline, a higher percentage with peripheral vascular disease at baseline and a higher percentage of current smokers in the background SU stratum compared with background MET. The assignment to background stratum was not randomized, so determinations by the subject's treating physician could have contributed to the between-strata differences.

Table 5 RECORD: Baseline Characteristics by Study Stratum (ITT population)

	Background Metformin		Background Sulfonylurea	
	Rosiglitazone (N = 1117)	Sulfonylurea (N = 1105)	Rosiglitazone (N =1103)	Metformin (N = 1122)
Age (years)	57.0 (8.0)	57.2 (8.1)	59.8 (8.3)	59.7 (8.2)
Sex (male)	601 (53.8)	584 (52.9)	541 (49.0)	568 (50.6)
Race (white)	1105 (98.9)	1087 (98.4)	1095 (99.3)	1112 (99.1)
Ischemic heart disease Stable angina Myocardial infarction	171 (15.3) 105 (9.4) 50 (4.5)	164 (14.8) 86 (7.8) 62 (5.6)	212 (19.2) 122 (11.1) 54 (4.9)	225 (20.1) 144 (12.8) 52 (4.6)
Stroke	26 (2.3)	20 (1.8)	29 (2.6)	33 (2.9)
Transient ischemic attack	27 (2.4)	25 (2.3)	24 (2.2)	22 (2.0)
Peripheral vascular disease	80 (7.2)	96 (8.7)	117 (10.6)	117 (10.4)
Heart failure	4 (0.4)	4 (0.4)	8 (0.7)	5 (0.4)
Retinopathy	73 (6.5)	77 (7.0)	141 (12.8)	157 (14.0)
Current smoker	199 (17.8)	194 (17.6)	164 (14.9)	149 (13.3)
Microalbuminuria/proteinuria[1]	225 (20.1)	192 (17.4)	215 (19.5)	219 (19.5)
Duration from diabetes diagnosis (yr)	6.1 (4.2)	6.3 (4.4)	7.9 (5.5)	7.9 (5.2)
Weight (kg)	93.5 (16.5)	93.3 (16.3)	85.0 (14.5)	84.3 (14.4)
Body mass index (kg/m^2)	32.8 (5.0)	32.7 (5.2)	30.3 (4.1)	30.1 (4.3)
HbA_{1c} (%)	7.8 (0.7)	7.8 (0.7)	8.0 (0.7)	8.0 (0.7)
Fasting plasma glucose (mg/dL)	171.1 (37.8)	171.1 (37.8)	183.7 (46.8)	182.0 (41.4)
Systolic blood pressure (mmHg)	140 (16)	139 (16)	138 (15)	138 (15)
Diastolic blood pressure (mmHg)	84 (9)	83 (9)	82 (8)	82 (8)
LDL cholesterol (mmol/L)	3.2 (0.9)	3.2 (0.9)	3.4 (0.9)	3.4 (0.9)
HDL cholesterol (mmol/L)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Triglyceride (mmol/l)	2.3 (1.3)	2.4 (1.5)	2.3 (1.7)	2.2 (1.6)

n (%) or mean (SD)

1. Microalbuminuria defined as albumin:creatinine ratio >2.5 mg/mmol (men), >3.5 mg/mmol (women)

4.4. Disposition

A total of 4447 subjects were randomized and received at least one dose of study medication, 2222 subjects on background MET were randomized to receive additional RSG (1117) or SU (1105), and 2225 subjects on background SU were randomized to receive additional RSG (1103) or MET (1122). The proportion of subjects who completed CV follow-up to the final visit (approximately 82%) and who completed follow-up for the primary endpoint (approximately 89%) was comparable between the combined RSG and MET/SU groups. Approximately 11% of subjects withdrew from CV follow-up without having a primary event and 2.9% had unconfirmed vital status at study end, and these proportions were comparable between treatment groups.

A summary of the follow-up status is given in Table 6, and cardiovascular/vital-status follow-up is shown graphically in Figure 9.

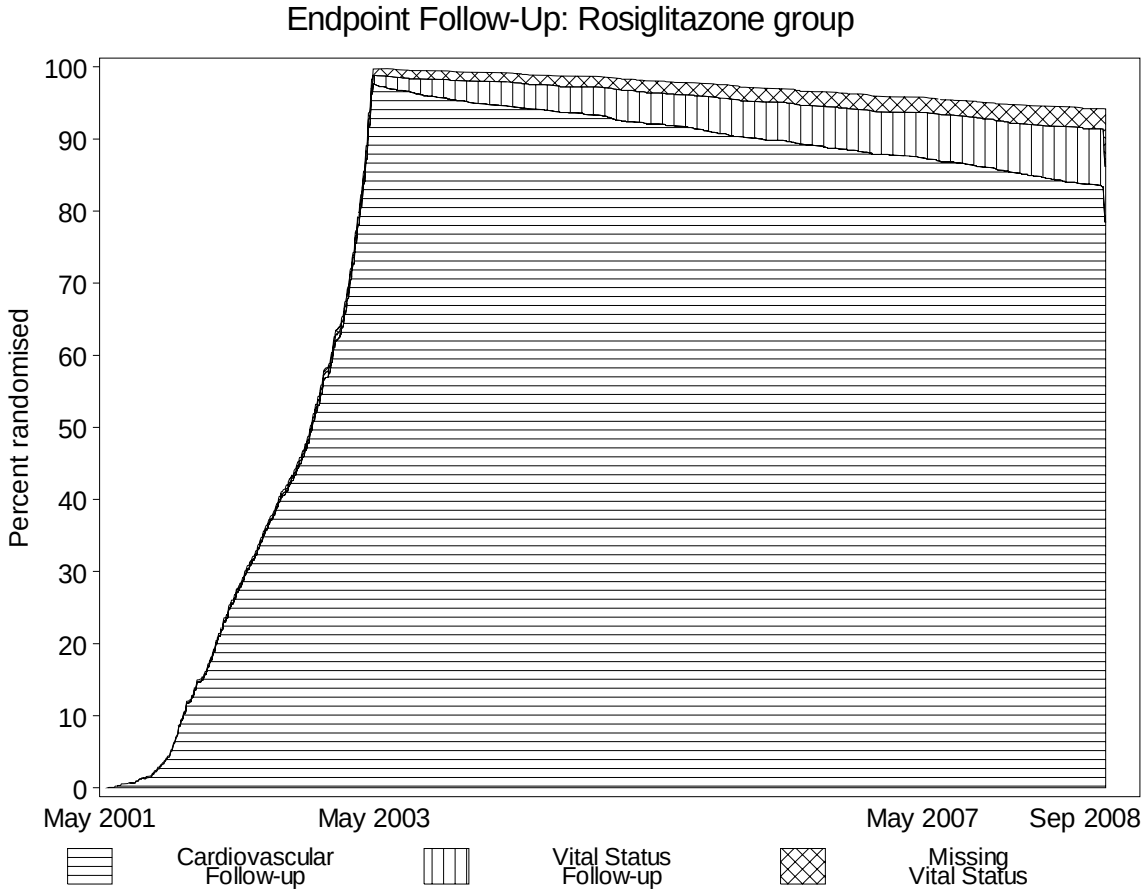
Table 6 RECORD: Summary of Follow-up for Vital Status and CV Events (ITT population)

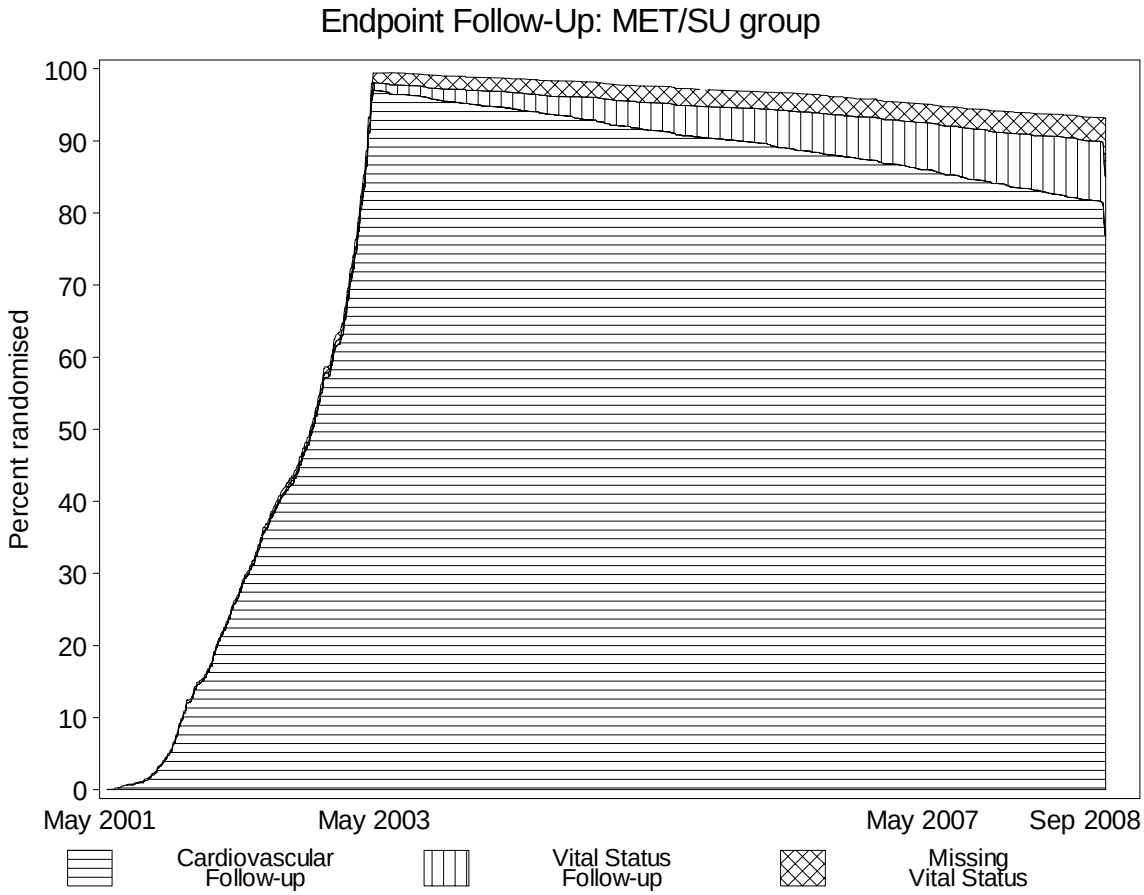
	Treatment Group		
Completion Status	Combined RSG	MET/SU	Total
n (%)	(N=2220)	(N=2227)	(N=4447)
Completion status for CV follow-up			
Completed CV follow-up for primary endpoint[1]	1977 (89.1)	1968 (88.4)	3945 (88.7)
Completed CV follow-up to final visit	1835 (82.7)	1798 (80.7)	3633 (81.7)
Died[2]	111 (5.0)	139 (6.2)	250 (5.6)
Withdrew from CV follow-up after having a primary endpoint	31 (1.4)	31 (1.4)	62 (1.4)
Withdrew from CV follow-up without having a primary endpoint	243 (10.9)	259 (11.6)	502 (11.3)
Vital status at study end for subjects withdrawn from CV follow-up			
Alive	189 (8.5)	205 (9.2)	394 (8.9)
Died	25 (1.1)	18 (0.8)	43 (1.0)
Vital status unconfirmed[2]	60 (2.7)	67 (3.0)	127 (2.9)

1. Either: at least one adjudicated event; no event and completed CV follow-up to study end; no event and follow-up terminated due to non-CV death.
2. During study end window (24 Aug 2008 to 26 Dec 2008)

The graphs shown in Figure 9 depict the proportion of patients being followed for events at any given time (randomization occurred May 2001 to May 2003), through to commencement of the study closeout in September 2008. The areas under the curves represent total patient follow-up time, highlighting that for each treatment group the overall level of cardiovascular/vital status follow-up was a very high proportion of the maximum possible follow-up that could have been observed (with 7.2% of patient-years lost for CV events and 2.0% lost for vital status).

Figure 9 **RECORD: Percentage of ITT Subjects being followed for Cardiovascular Events and Vital Status throughout the Duration of RECORD**





The majority of CV follow-up patient years was on randomized treatment (approximately 88% for RSG [75% dual therapy, 13% triple therapy] and 83% for MET/SU). Furthermore, over 85% of subjects had > 5 years of on-treatment follow-up.

Table 7 summarizes the average person-years for CV events.

Table 7 RECORD: Summary of Average Person-years Follow-up for CV Events

Person-years Follow-up	Treatment Group		Total
	RSG (N=2220)	MET/SU (N=2227)	(N=4447)
Mean ± SD	5.56±1.48	5.51±1.53	5.53±1.50
Median	5.74	5.72	5.72
Range	0-7.5	0-7.5	0-7.5

4.5. Process for Collection and Adjudication of Endpoints

The process for collection and adjudication of endpoints was designed to:

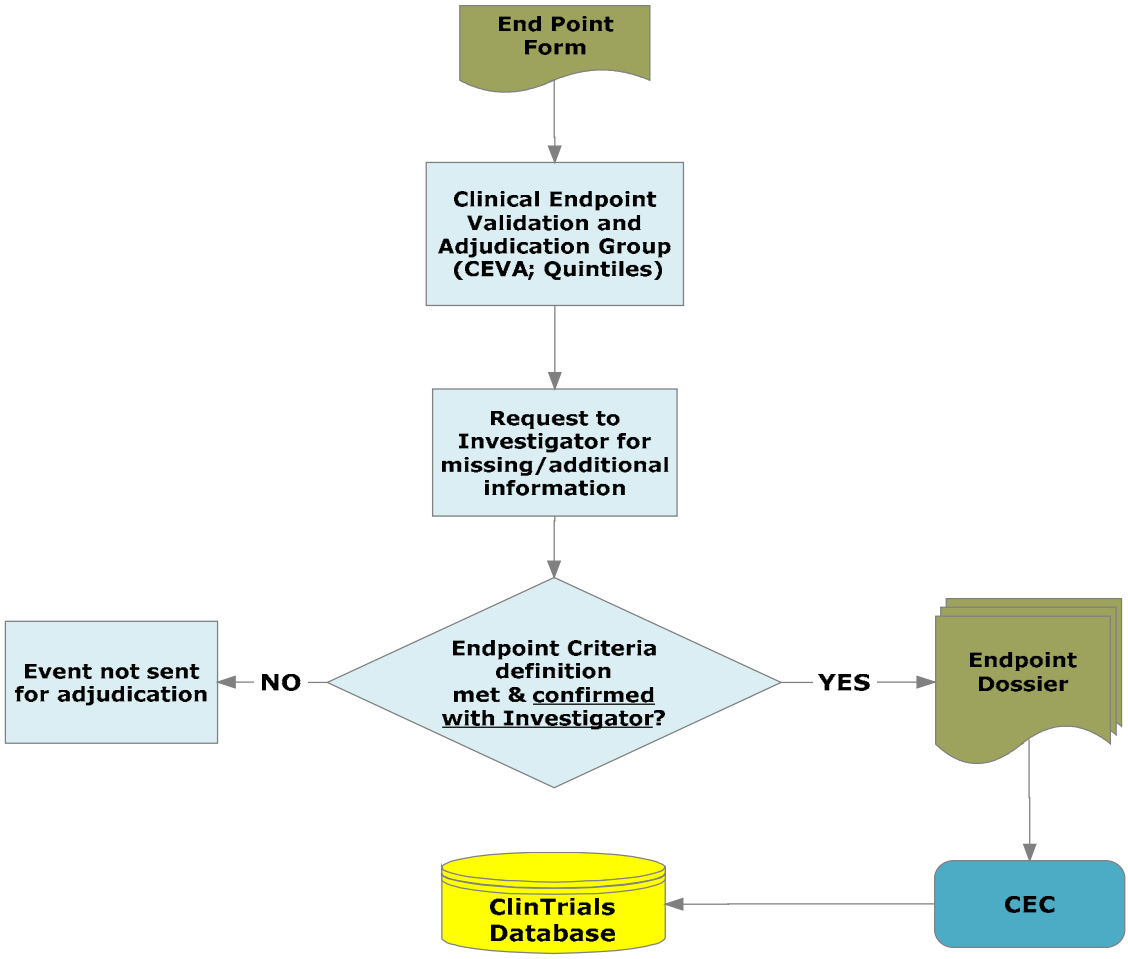
- Provide independent, unbiased, and expert review of clinical endpoint events which occurred during the RECORD trial;

- Ensure unified and unambiguous event evaluation practices across the RECORD trial, by verifying the application of standardized event criteria, per protocol specifications;
- Compensate for regional diversity in medical practice in the area of endpoint evaluation and classification, thereby reducing the impact of this diversity on efficacy analysis.

Potential Clinical Endpoints of CV hospitalization and/or Death, identified by the investigator, were sent to the CEC Co-ordinating Centre (also known as the Clinical Endpoint Validation and Adjudication group–CEVA) with study treatment identifiers removed in order to maintain the blind of the CEC. The CEC Co-ordinating Centre was managed by Quintiles (contract research organization).

An overview of the process followed once a potential endpoint was received at the CEC Coordinating Centre (Figure 10).

Figure 10 RECORD: Overview of the CEVA process



Once the relevant endpoint data was received at the CEC Coordinating Centre at Quintiles, Dublin it was reviewed to determine whether the event met the protocol defined criteria of a potential endpoint. The Endpoint dossier then was submitted to the CEC.

The Endpoint dossier was submitted to two paired CEC members (selected at random) for a first level review. If the event was a potential stroke/TIA endpoint it was also sent to the neurologist on the CEC. If the reviewers disagreed on the outcome of the adjudication, the disputed endpoint was sent for full CEC review.

An endpoint's adjudication provided by the CEC to the CEC Co-ordinating Centre was considered the official and final classification of the endpoint. In some circumstances events were readjudicated by the CEC. Readjudications were performed for CV procedure events following an amendment to the definition of CV procedure endpoints in the CEC charter at the request of the Steering Committee. Following this amendment non-urgent (planned) CV procedures were no longer considered to be endpoints. In addition some events were readjudicated for other reasons such as the availability of new information on the event.

4.5.1. Safeguards in Place to ensure all Potential Endpoints were reported

4.5.1.1. Reporting of Endpoints by Subjects

To ensure that subjects reported all potential endpoints to the investigators, targeted questions were used to solicit endpoints at regular patient visits. In addition, investigators were given regular training about endpoint data collection.

An endpoint sweep was performed in 2005 at the request of the Steering Committee to determine whether under-reporting of events was contributing to the low event rate seen in RECORD. Following completion of the endpoint sweep, the Steering Committee determined that the sweep was successful in demonstrating that the sites were adequately collecting and reporting endpoint data.

4.5.1.2. Reporting of Endpoints by Investigators

To ensure that investigators reported all potential endpoints to the CEC Co-ordinating Centre, clinical monitors performed source document verification at sites to identify any potential, un-reported endpoints. In addition clinical team leaders reviewed monitoring visit reports with a focus on serious adverse events (SAEs), as these events could be potential endpoints requiring further follow up via the site monitors.

All serious adverse events had to be captured in the case report form on designated SAE pages, whether or not they were also deemed by the investigator to be potential study endpoints. As a further safeguard, reconciliations were performed on a regular basis by medically qualified Clinical Team Leaders within Quintiles between reported SAEs and reported endpoints, to identify any potential, un-reported endpoints. At the end of the study, a full review /reconciliation of SAEs and endpoints was performed by Clinical Team Leader/Project Manager and GSK physicians in a blinded fashion. Reconciliation

was also performed to confirm that all CV events submitted for adjudication had a matching adjudication result in the clinical database.

4.6. Cardiovascular Outcome Results

4.6.1. Primary Endpoint–Cardiovascular Hospitalization or Cardiovascular Death

The event rate for the primary endpoint of CV hospitalization or CV death was 28 per 1000 patient-years. The primary endpoint occurred in 321 and 323 patients assigned to the RSG group and control groups, respectively (HR 0.99, 95% CI 0.85-1.16) (Table 8). The protocol pre-specified criterion of non-inferiority was met (upper 95% confidence limit <1.2; non-inferiority p-value=0.016).

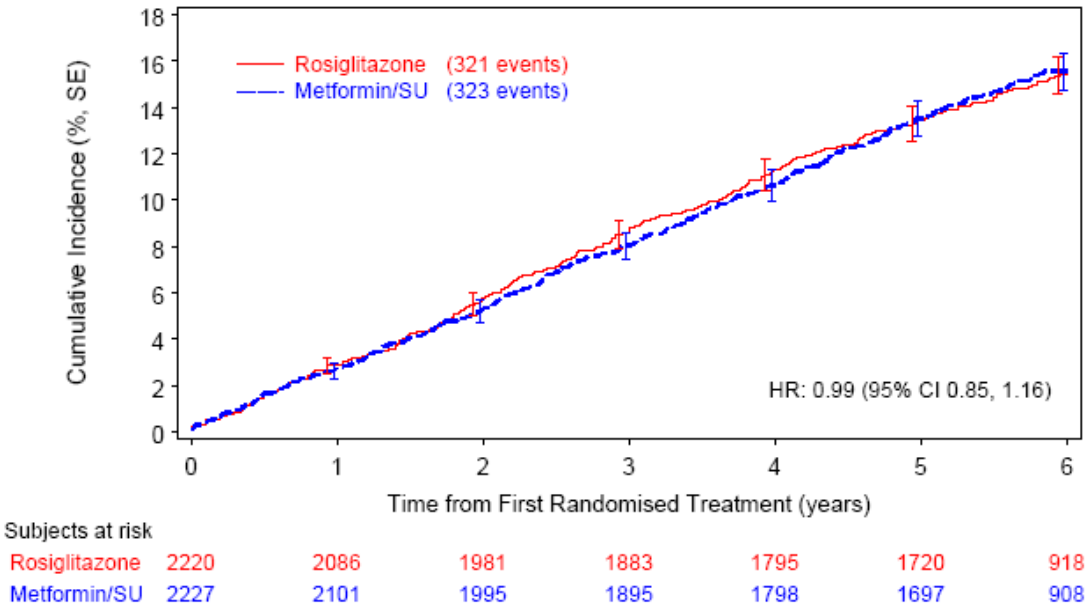
Table 8 RECORD: Occurrence of CV Death or CV Hospitalization (ITT population)

	Treatment Group	
Time to First Occurrence of	RSG	MET/SU
CV Death/Hospitalization	(N=2220)	(N=2227)
No. (%) subjects with an event	321 (14.5)	323 (14.5)
Incidence: rate/100 PY[1] (95% CI)	2.79 (2.49-3.11)	2.81 (2.51-3.13)
Hazard ratio[2] , (95% CI); Non-inferiority p-value[3]	0.99 (0.85-1.16); p=0.0164	
Absolute rate difference/100PY[1]	-0.02 (-0.45-0.41)	

1. Person-years up to first primary event/censoring.
2. Based on Stratified (by background stratum) Cox's Proportional Hazards Model: Time=Treatment; HR is relative to MET/SU
3. p <0.05 is equivalent to the upper 95% confidence limit for the true hazard ratio < 1.2.

The cumulative incidence over time of the primary endpoint is displayed in Figure 11.

Figure 11 RECORD: Cumulative Incidence of Time to First Occurrence of CV Death or CV Hospitalization (ITT population)

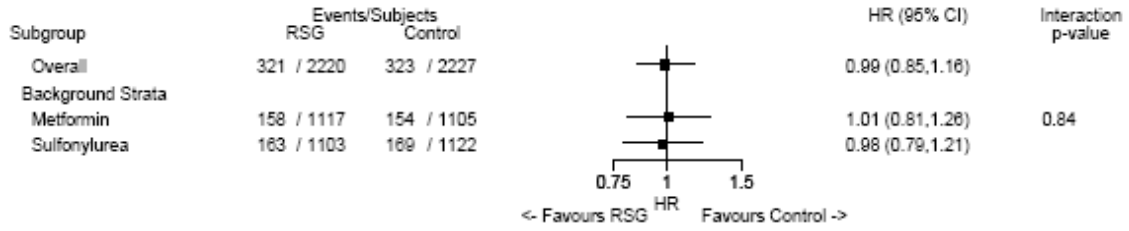


4.6.1.1. Sensitivity Analyses of Primary Endpoint

A series of pre-specified sensitivity analyses were performed on the primary endpoint. A per-protocol analysis (including patient follow-up 30 days after transfer from dual therapy) gave similar results to the primary Intention-to-Treat (ITT) analysis (HR 1.02, 95% CI 0.85-1.21). Cardiovascular deaths or hospitalizations were 240 on RSG and 260 on control, with exposures of 8905 patient-years and 9818 patient-years, respectively. An additional sensitivity analysis excluding some cardiovascular events likely not of atherosclerotic origin (e.g., ablation/pacemaker, aortic prosthesis thrombosis, deep vein thrombosis) gave similar results (HR 0.97, 95% CI 0.82-1.14).

For patients on background MET at entry to the study, the comparison RSG with SU (HR 1.01, 95% CI 0.81-1.26) was similar to the overall result (Figure 12). For patients on background SU, the comparison of RSG with MET (HR 0.98, 95% CI 0.79-1.21) was also similar to the overall result. There was no evidence of a treatment-by-stratum interaction (p=0.84).

Figure 12 RECORD: Hazard Ratios for Rosiglitazone Relative to Control for Time to First Occurrence of CV Death or CV Hospitalization, Overall and By Stratum (ITT population)



1. Note: For the background MET stratum, control is SU. For the background SU stratum, control is MET

4.6.2. Secondary Cardiovascular Endpoints

The hazard ratios (HR) and rate difference per 100 PY for the secondary CV outcomes (additional composite and individual endpoints) are presented in Table 9, Figure 13, and Figure 14 with results of the primary outcome included for reference.

Table 9 RECORD: Primary and secondary cardiovascular endpoints–overall results

Endpoint	RSG N=2220	MET/SU N=2227	Hazard Ratio (95% CI)	Rate difference per 100 PY	P value
Primary endpoint					
CV death or CV hospitalization	321	323	0.99 (0.85-1.16)	-0.02 (-0.44-0.42)	0.93
Secondary endpoints[1]					
All-cause Death	136	157	0.86 (0.68-1.08)	-0.17 (-0.43-0.09)	0.19
CV Death	60	71	0.84 (0.59-1.18)	-0.09 (-0.27-0.09)	0.32
MACE (CV death, Acute MI or Stroke)	154	165	0.93 (0.74-1.15)	-0.10 (-0.39-0.19)	0.50
Acute MI[2]	64	56	1.14 (0.80-1.63)	0.06 (-0.11-0.24)	0.47
Stroke[1]	46	63	0.72 (0.49-1.06)	-0.14 (-0.31-0.02)	0.10
Congestive heart failure[2]	61	29	2.10 (1.35-3.27)	0.26 (0.11-0.41)	0.001

1. All CV endpoints are represented here except for the combined CV/Microvascular endpoint.
2. Fatal and non-fatal

CV=cardiovascular, MI= Myocardial infarction

Figure 13 RECORD: Kaplan-Meier Plots of Time to First Occurrence for Key Secondary Endpoints

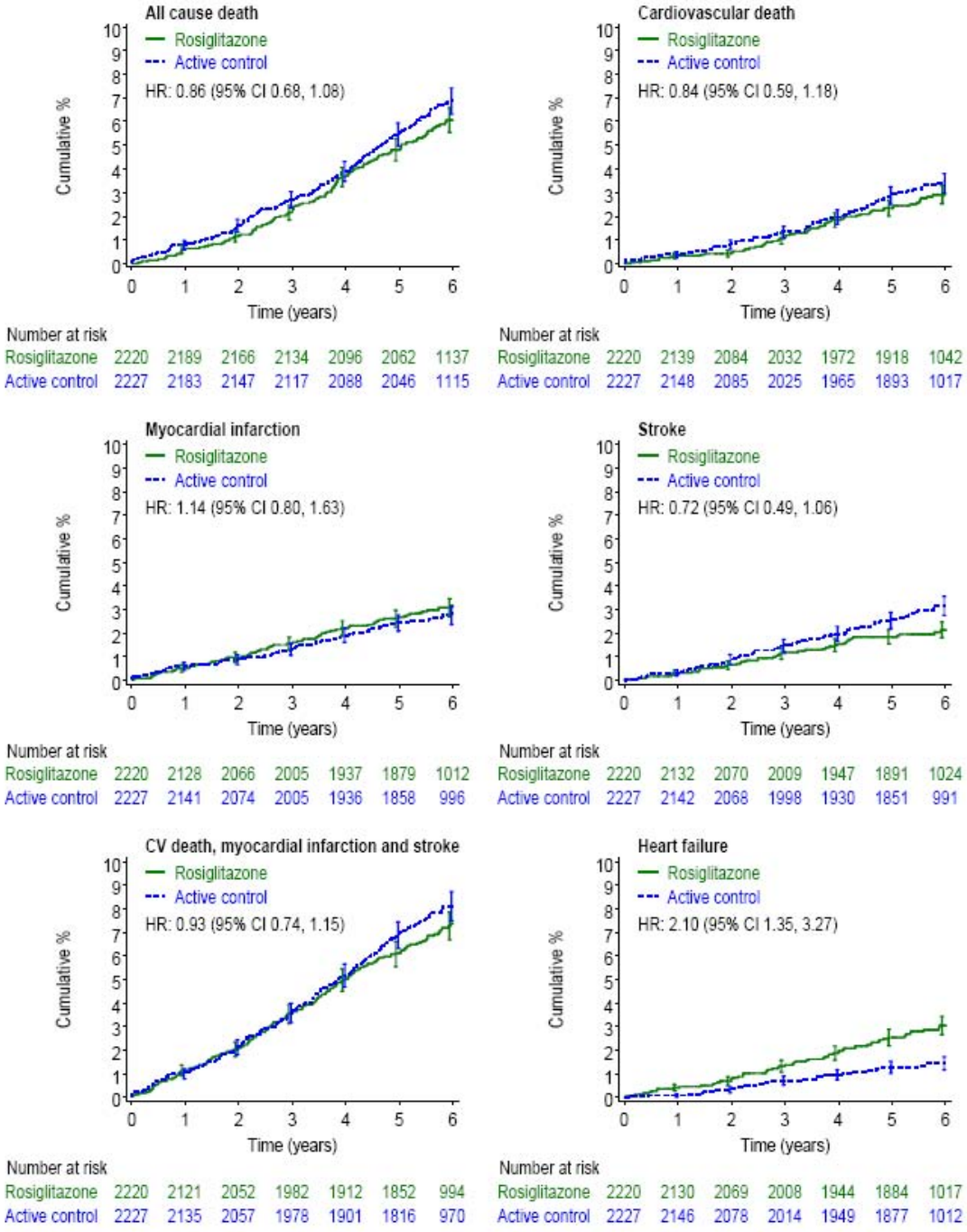
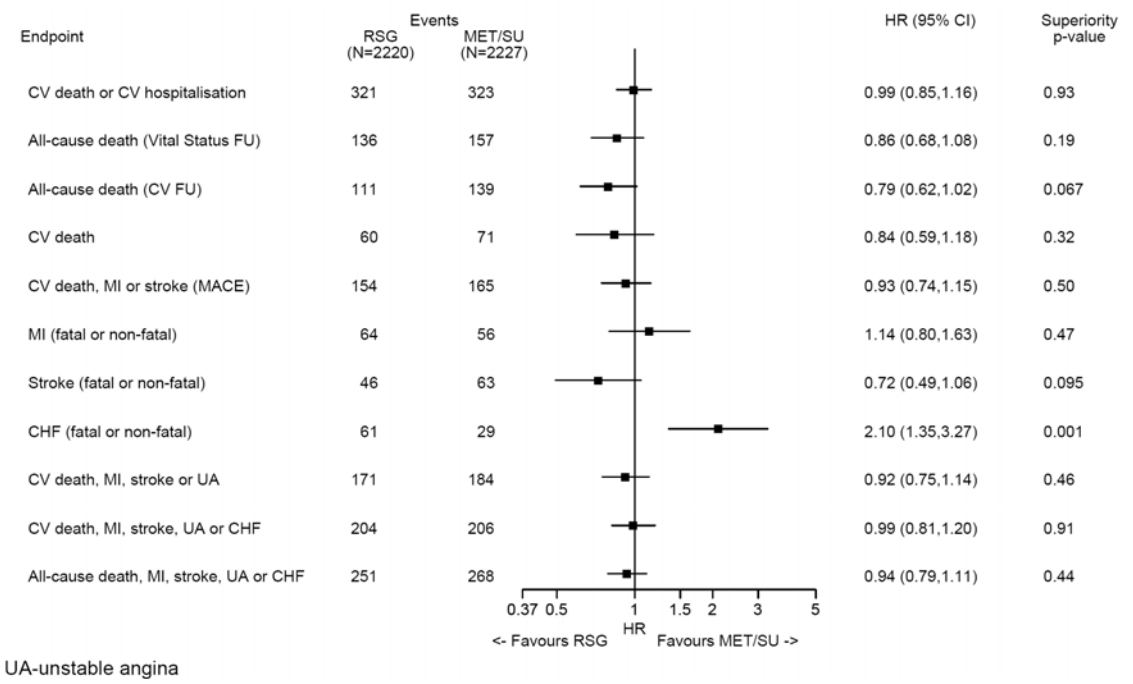


Figure 14 RECORD: Forest Plot of Hazard Ratios (95% CIs) for Primary and All Secondary CV Endpoints (ITT population)



There were no significant differences between groups for secondary endpoints related to CV events or mortality except for CHF. The incidence of CHF was significantly greater among subjects in the RSG group compared to MET/SU. The increase in the risk of heart failure is consistent with data from prior randomized trials and product labeling. The HR for the secondary composite endpoint of MACE, a commonly accepted measure of ischemic CV morbidity and mortality, was consistent with the primary endpoint and the upper bound of the 95% CI similarly excluded a 20% increase in risk for RSG compared to MET/SU.

There were fewer events of CV death and all-cause death in the RSG group compared to MET/SU. The HR was <1 for both endpoints, with CIs that spanned unity: CV death [HR 0.84, 95% CI (0.59-1.18)], all-cause death [HR 0.86, 95% CI (0.68-1.08)]. There were more events of MI in the RSG group compared to MET/SU [HR 1.14, 95% CI (0.80-1.63)] and fewer events of stroke in the RSG group compared to MET/SU [HR 0.72 (95% CI 0.49-1.06)].

The total number of CV hospitalizations (counting separately second and any subsequent hospitalizations for the same patient) was similar between the groups, with the RSG group reporting more CHF, more MI, fewer strokes, fewer invasive CV procedure hospitalizations, and fewer events of amputation of extremities (Table 10).

Table 10 RECORD: Total Number of Subjects with Events (Number of Events) for Various Cardiovascular Hospitalizations or Death, Independent of whether Part of the Primary Endpoint (ITT Population)

	RSG N=2220	MET/SU N=2227
Deaths		
All cause	136	157
Cardiovascular death	60	71
Sudden death	8	12
Myocardial infarction	7	10
Congestive Heart failure	10	2
Stroke	0	5
Other acute vascular event	1	5
Other cardiovascular mortality	6	4
Unattributed cause[1]	28	33
Cardiovascular hospitalization	288 (483)	284 (490)
Invasive cardiovascular procedures	85 (99)	100 (116)
Myocardial infarction	60 (66)	52 (57)
Stroke	46 (51)	63 (67)
Congestive Heart failure	57 (69)	29 (36)
Atrial fibrillation	35 (39)	36 (47)
Angina pectoris	25 (31)	26 (29)
Unstable angina pectoris	24 (28)	24 (28)
Transient ischemic attack	10 (10)	10 (10)
Amputation of extremities	5 (6)	15 (23)
Other CV hospitalizations	71 (84)	66 (77)

1. Fatal events of unknown cause were considered to be of CV origin unless there was good evidence to adjudicate them otherwise.

Within the separate causes of CV death, comparing RSG vs. MET/SU, there were: fewer sudden deaths (8 vs. 12); fewer deaths due to MI (7 vs. 10), more deaths due to CHF (10 vs. 2), more deaths due to other cardiovascular mortality (6 vs 4), fewer deaths due to stroke (0 vs. 5) and fewer deaths due to other acute vascular events (1 vs. 5). Limited interpretation can be made for individual causes of death due to the low event counts. While there were more deaths due to CHF (and more cases of CHF overall) in the RSG group, there was no evidence of an increase in overall risk of CV death as noted above.

4.6.3. *Post hoc* analyses of composite cardiovascular endpoints

After the code break for the study and the completion of the pre-specified study analyses, three additional composite endpoints were examined to describe a broader range of coronary events than just myocardial infarction (Figure 15). They were:

- Any acute coronary syndrome (ACS)
  (defined as fatal MI, sudden death, hospitalization for cardiac arrest, hospitalization for acute MI, hospitalization for unstable angina).

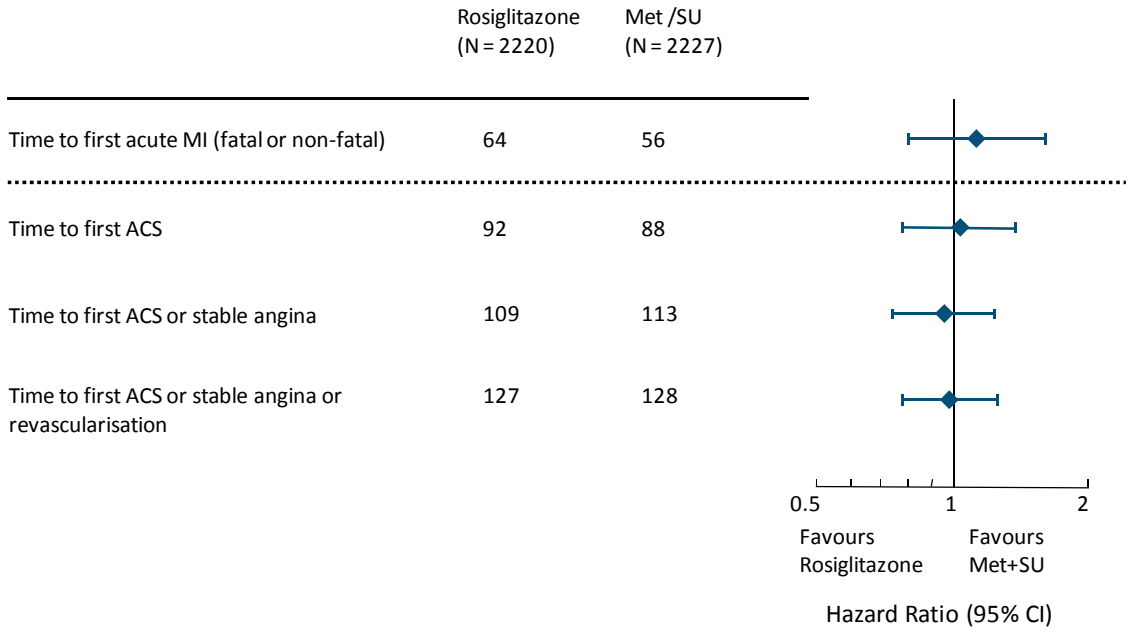
- Any ACS or other angina
  (ACS plus "other" cardiovascular hospitalization attributed to angina pectoris)
- Any ACS, other angina or coronary revascularization:
  (as above plus percutaneous coronary intervention or CABG)

An ACS event occurred in 92 (4.1%) patients randomized to RSG and 88 (4.0%) patients randomized to MET/SU. The time to first event analysis yielded an HR of 1.05 (95% CI 0.78 to 1.40), p=0.77.

An ACS or hospitalization for other angina event occurred in 109 (4.9%) patients randomized to RSG and 113 (5.1%) randomized to MET/SU. The HR was 0.96 (95% CI 0.74 to 1.25), p=0.78.

An ACS, hospitalization for other angina or coronary revascularisation event occurred in 127 (5.7%) patients randomized to RSG and 128 (5.7%) randomized to MET/SU. The HR was 0.99 (95% CI 0.78-1.27), p=0.94.

Figure 15 RECORD: Forest Plot of Hazard Ratios (95% CIs) for MI and for *post hoc* ACS Composite Endpoint Analyses (ITT population)



These analyses did not show a statistically significant increase in coronary events with RSG compared to MET/SU. This was true for the pre-specified secondary endpoint of myocardial infarction as well as the *post hoc* expanded composites which included other coronary events.

4.6.4. Other Clinical Secondary Endpoints

Microvascular (diabetes related) endpoints comprised eye, renal and foot microvascular complication. These events were investigator-reported and not adjudicated. There was no significant difference in the time to first CV (primary event) or microvascular event (HR: 0.94 (95% CI: 0.81-1.08); p=0.4). The incidence of microvascular events was

lower in the RSG group compared to MET/SU, however, there was no significant difference [59 (2.7%) vs 78 (3.5%) subjects, HR 0.75, 95% CI (0.54-1.05); p=0.097)]. No renal microvascular events (defined as end stage renal events) were reported.

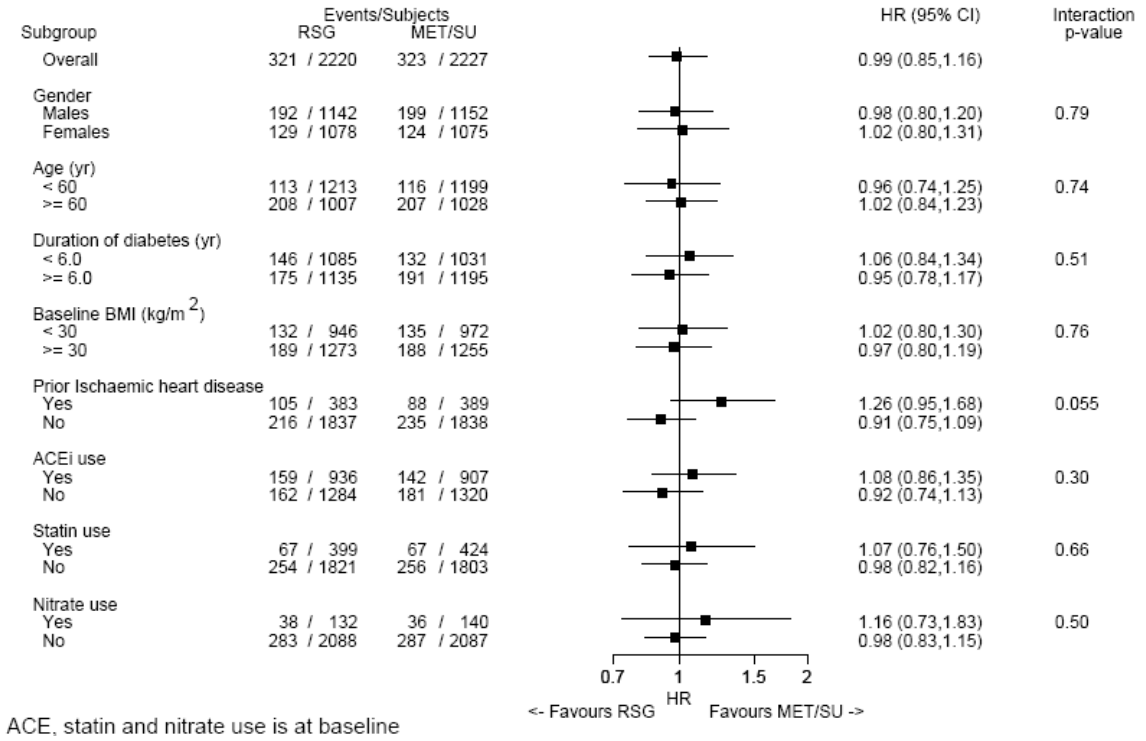
4.6.5. Subgroup Analyses

A number of subgroup analyses of the primary endpoint were pre-specified. Some of these subgroups were based on previous RSG studies that have suggested different results in subgroups, e.g. use of nitrates from the ICT analysis, potential interaction with ACE inhibitors in the DREAM trial. The results of these subgroup analyses are shown in Figure 16.

The lower than expected CV event rate and small numbers of subjects in some subgroups make a definitive assessment difficult. However, the results in the subgroups were mostly consistent with the results for the overall population and, in particular, no interactions were seen in subjects on nitrates (interaction p=0.50) or ACE-inhibitors (interaction p=0.30) at baseline.

Only for prior history of IHD was there a suggestion of heterogeneity for the primary outcome (interaction p-value=0.055). Subjects with prior IHD had a HR for the time to first occurrence of adjudicated CV death or CV hospitalization for RSG relative to MET/SU of 1.26 (95% CI 0.95-1.68), whereas for subjects without a history of prior IHD, the HR was 0.91 (95% CI 0.75-1.09). A number of *post hoc* analyses were performed to explore this interaction in further detail (described below).

Figure 16 RECORD: Forest Plot of Hazard Ratios (95% CIs) for Time to First Occurrence of Adjudicated CV Death/CV Hospitalization by Key Subgroups (ITT population)



Since prior IHD is comprised of several medical history terms (prior MI, prior stable angina, etc.) the component sub-types were examined (Table 11). However, a specific sub-type of prior IHD with elevated relative risk of a primary endpoint event could not be identified. For example, for subjects with prior IHD in the RSG group, neither the presence of baseline stable angina nor prior MI carried an increased risk for a primary endpoint event compared to corresponding MET/SU subjects. More subjects in the RSG group (48 vs.22) with other types of prior IHD had CV events during the study (described in the Table 11 as "IHD Other" since these events were captured as verbatim terms on the other medical and surgery history page of the CRF rather than as pre-specified terms on the CV medical history page). When examined by background therapy stratum, the imbalance in the primary endpoint for subjects with prior IHD appears to be accounted for by the differences in the SU stratum, and within this stratum by terms within 'other CV hospitalizations'.

Table 11 RECORD: CV Death or CV Hospitalization in Subjects with Ischemic Heart Disease at Baseline (ITT population)

CV Death/Hospitalization	Treatment Group	
	RSG (N=2220) n/N	MET/SU (N=2227) n/N
All Subjects	321/2220	323/2227
Subjects with Prior IHD	105/383	88/389
Angina (Stable)	59/227	56/230
Myocardial Infarction	37/104	35/114
Coronary Angioplasty (±Stent)	22/68	22/66
Unstable Angina	8/20	11/30
Ischemic Heart Disease- Other*	48/154	22/138

*Other may include the terms atherosclerosis, atherosclerosis heart, cardiovascular disease
Note: subjects may be included in more than one category of baseline IHD

A breakdown of the components of the primary endpoint (Table 12) revealed that while the incidence of heart failure was higher in the RSG group for subjects both with and without prior IHD (giving similar relative risks of 2.16 and 2.10 respectively in these two sub-groups), other reasons for CV hospitalization or CV death showed no evidence of such excess.

Table 12 RECORD: CV Endpoints by Baseline History of Ischemic Heart Disease, Overall Groups (ITT population)

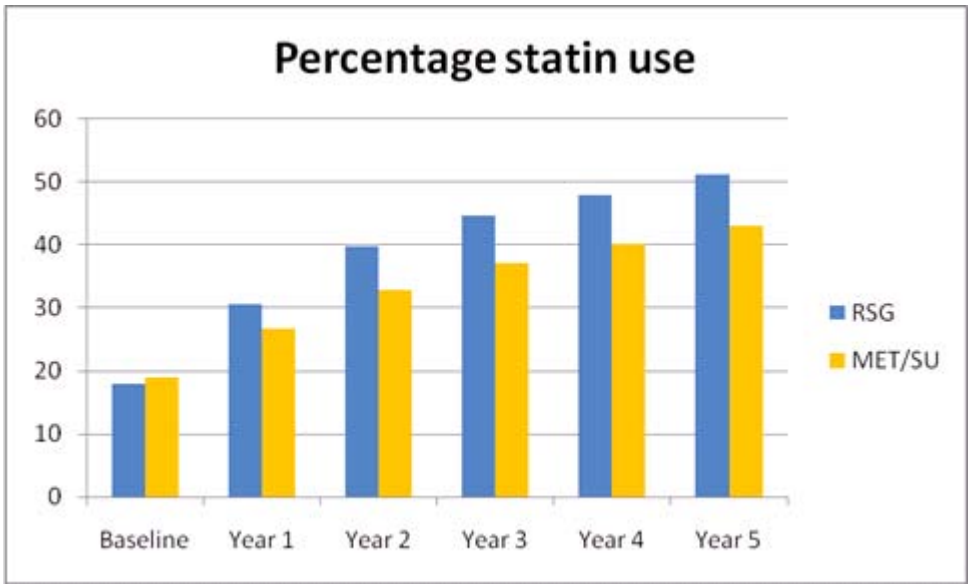
Subjects with CV Events				
	Prior IHD		No Prior IHD	
	RSG (N=383)	MET/SU (N=389)	RSG (N=1837)	MET/SU (N=1838)
CV death/hospitalization	105	88	216	235
All-cause death	43	45	93	112
CV death	23	24	37	47
MACE	47	43	107	122
Acute MI (fatal/non-fatal)	20	19	44	37
Stroke (fatal/non-fatal)	10	9	36	54
CHF (fatal/non-fatal)	17	8	44	21
Unstable angina	15	10	9	14

4.7. Statin Use in RECORD

Lipid lowering therapy was permitted in RECORD to ensure patients could be treated to prevailing European guidelines. Simvastatin and atorvastatin were by far the most widely used statins. The mean doses of simvastatin and atorvastatin at 5 years were similar for RSG and control; for simvastatin 24.3 mg vs 23.1 mg and for atorvastatin 21.0 mg vs 18.9 mg. Figure 17 shows that the proportion of patients with concomitant statin use was higher in the RSG group beginning in Year 1 onwards reaching a maximum difference of 8.1% of patients by Year 5. As statin use was higher in the RSG group,

consideration has been given as to whether this differential in the proportion of patients with statin use could contribute to differences in atherosclerotic events. Assuming that statins reduce atherosclerotic events by 25%, then even if the 8.1% difference prevailed from Day 1 of the study, the HR for atherosclerotic events would not be reduced by more than 2% (0.25 x 0.08=0.02) [Home, 2009]. An increase in the HR for the primary endpoint of 2% would not have altered the conclusion on non-inferiority.

Figure 17 RECORD: Percentage of Patients with Concomitant Statin Use Over Time, in patients completing to the end of each study year



4.8. Safety results

The serious adverse events represent both CV and non-CV events as reported by the investigators prior to any adjudication. Table 13 summarises investigator-reported serious adverse events reported in 20 or more patients in either treatment group and additionally events identified prospectively to be of particular interest in the context of TZD therapy.

Table 13 RECORD: Patients with Serious Adverse Events*

	RSG N=2220	MET/SU N=2227	P
Infections	139 (6.3%)	157 (7.0%)	0.32
Pneumonia	41 (1.8%)	35 (1.6%)	0.56
Malignancies	126 (5.7%)	148 (6.6%)	0.20
Prostate cancer**	15 (1.3%)	21 (1.8%)	0.41
Breast cancer**	11 (1.0%)	17 (1.6%)	0.34
Colon cancer	10 (0.5%)	14 (0.6%)	0.54
Pancreatic cancer	2 (<0.1%)	13 (0.6%)	0.0074
Bladder cancer	6 (0.3%)	5 (0.2%)	0.99
Gastrointestinal disorders	133 (6.0%)	119 (5.3%)	0.39
Myocardial infarction	74 (3.3%)	67 (3.0%)	0.59
Myocardial ischemia	14 (0.6%)	10 (0.4%)	0.54
Unstable angina	39 (1.8%)	38 (1.7%)	0.99
Angina pectoris	48 (2.2%)	37 (1.7%)	0.27
Coronary artery disease	24 (1.1%)	33 (1.5%)	0.29
Atrial fibrillation	33 (1.5%)	34 (1.5%)	1.00
Heart failure	82 (3.7%)	42 (1.9%)	0.0003
Cerebrovascular accident	43 (1.9%)	63 (2.8%)	0.064
Transient ischemic attack	22 (1.0%)	25 (1.1%)	0.78
Hypertension	19 (0.9%)	21 (0.9%)	0.89
Pulmonary embolism	10 (0.5%)	13 (0.6%)	0.68
Bone fracture	49 (2.2%)	36 (1.6%)	0.18
Osteoarthritis	29 (1.3%)	24 (1.1%)	0.58
Non-cardiac chest pain	21 (0.9%)	19 (0.9%)	0.89
Hyperglycemia	27 (1.2%)	55 (2.5%)	0.0027
Hypoglycemia	15 (0.7%)	6 (0.3%)	0.076
Macular edema	0 (0.0%)	0 (0.0%)	-
Cataract	17 (0.8%)	13 (0.6%)	0.57
Anemia	16 (0.7%)	10 (0.4%)	0.32

*Data are for serious adverse events reported for 20 or patients or those predefined as being of particular interest, in the context of thiazolidinedione therapy.
** For prostate cancer, data are for men only, and for breast cancer data are for women only.

The incidence of heart failure was significantly higher in patients allocated to RSG than in the MET/SU group. The incidence of myocardial infarction or stroke did not differ between the groups. The results of the SAE reports for CV events are consistent with the endpoint results. Overall incidence of malignancy or of specific tumor types, including bladder and colon cancer, did not differ in the two groups, but the incidence of pancreatic cancer was significantly less in the RSG group than in the MET/SU group.

Hyperglycemia was less frequent but hypoglycemia more frequent in the RSG group than in the MET/SU group. The incidence of all adverse events of hypoglycemia (serious and non-serious) was higher in the SU-containing groups (Met+SU 197 patients, 18%; SU+Met 148 patients, 13%; SU+RSG 175 patients, 16%) than in the non-SU-containing combination of RSG and MET (57 patients, 5%). Macular edema was not reported as a

serious adverse event. Non-serious adverse events of macular edema were reported in 7 patients on RSG and 3 on MET/SU control.

There was a higher incidence of subjects with bone fractures in the RSG group (8.3%) than in the MET/SU group (5.3%). The majority of fractures were reported in the upper limbs and distal lower limbs and the relative risk of fractures appeared to be higher in females (11.5% RSG vs 6.3% MET/SU) than in males (5.3% RSG vs 4.3% MET/SU). Data on fractures from RECORD are consistent with the observations from ADOPT which are discussed in Section 2.7.2

4.9. Discussion

There have been several questions raised about the RECORD study, involving the low CV event rate, open label design, a broad cardiovascular primary endpoint, duration of CV follow-up, and patient time lost to follow-up, that are important to consider.

Despite a much lower than expected event rate, the number of primary events (644) proved sufficient to declare non-inferiority per the protocol pre-specified margin agreed with CHMP (1.20) because the point estimate for the hazard ratio for the primary endpoint was close to 1.00. There were sufficient events of heart failure to confirm the increased risk of heart failure with RSG therapy. There were insufficient cases of myocardial infarction to establish whether rosiglitazone affects this outcome. There were eight more patients with a fatal or non-fatal myocardial infarction in the rosiglitazone group, but three fewer with a fatal myocardial infarction (seven on rosiglitazone, 10 on control).

The study was by necessity open label; to minimize the potential for bias the adjudication of events was performed blind to the knowledge of treatment allocation. The use of a blinded adjudication process and the choice of clinically important, hard endpoints (cardiovascular events leading to hospitalization or death), together with the extent of follow-up (mean 5.5 years; 24,610 patient-years) represent enhanced strength of the CV outcome data from RECORD compared to the rosiglitazone studies that preceded it.

To address the criticism that the primary endpoint may have been overly-inclusive, a further pre-specified sensitivity analysis was performed which excluded events unlikely to be of atherosclerotic origin. This resulted in an HR of 0.97 and 95% CI 0.82-1.14.

Discontinuation of RSG treatment resulted in 88% of patient-years' cardiovascular follow-up being on rosiglitazone and 83% on MET/SU. A pre specified sensitivity analysis to test the stability of the primary endpoint to this effect (i.e. restricted to time on originally allocated dual therapy) yielded a very similar estimate for the HR (1.02) but, compatible with the smaller number of events included (500), a wider 95% CI (0.85-1.21). Importantly, at the end of the study vital status (alive or dead) was known in 97% of patients.

As previously noted, it was known, at the inception of the RECORD trial, that the design and conduct of long-term CV outcome studies in diabetes presented several challenges. Several steps were taken prospectively to address the challenges in RECORD. These steps included an endpoint sweep to confirm the low CV event rate, adjudicated

endpoints by an independent committee blinded to treatment, and pre-specified analyses were conducted to assess on-treatment effects and sensitivity to the definition of the primary endpoint. Therefore, despite these study challenges, the results from RECORD remain robust and reliable.

4.10. Conclusion

The RECORD study was prospectively designed to assess non-inferiority of RSG in combination with MET or SU compared with the combination of MET and SU for cardiovascular outcomes. The primary endpoint was the time to first cardiovascular hospitalization or cardiovascular death. The study employed a formal adjudication process for the assessment of cardiovascular outcome and studied 4447 patients with a mean follow-up of 5.5 years. The results of the RECORD study demonstrated that RSG does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs.

5. REVIEW OF ROSIGLITAZONE DATA FROM OTHER CARDIOVASCULAR TRIALS EXAMINING GLYCEMIC CONTROL STRATEGIES

A number of clinical trials (BARI 2D, ACCORD, and VADT) have addressed the effects of glycemic control on cardiovascular outcomes in established diabetic patients. Although these studies were not designed specifically to evaluate the CV safety of RSG, these NIH or Veteran Adminsitraion conducted trials provide important data because the trials are of long duration (3.5 to 5.6 years), enrolled over 14,000 patients, endpoints were adjudicated, and included a large number of patients at high risk of CV disease.

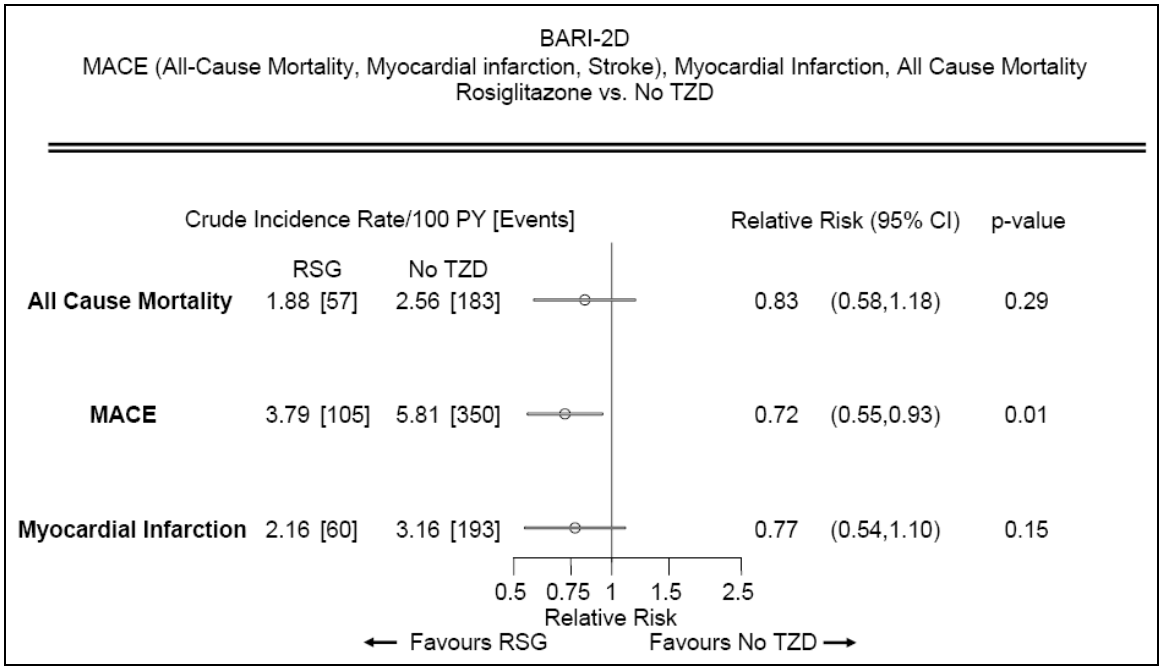
5.1. BARI 2D

The BARI 2D study was an international, NIH-sponsored, cardiovascular outcomes trial which included 2,368 patients with T2DM and all patients had established ischemic heart disease [BARI 2DStudy Group, 2009]. Using a 2x2 factorial design, patients were randomized to a diabetes treatment strategy (insulin-sensitization [IS] vs. insulin provision [IP]) and a coronary disease treatment strategy (prompt revascularization with intensive medical therapy vs. intensive medical therapy alone). The primary outcome was all-cause mortality and the principal secondary outcome was MACE (all-cause mortality, myocardial infarction or stroke). Patients assigned to the IS group were principally treated with MET and RSG and those assigned to the IP group with sufonylureas, secretagogues, and insulin. All patients were treated to a target HbA1c <7%. With respect to use of RSG in the trial, at the three-year follow-up, 55% of patients in the IS group were taking RSG compared with 3% in the IP group. Rosiglitazone use was at the discretion of the treating clinician.

At 5 years, results were similar between the IS and IP groups for the primary outcome of all-cause mortality (% survival: IS 88.2% vs. IP 87.9%; p=0.89) and for the principal secondary outcome of MACE (% event-free survival: IS 77.7% vs. IP 75.4%; p=0.13). Among subjects assigned to revasularization, the rate of MACE events was marginally lower in the IS group (IS 18.7% vs. IP 26.0%; p=0.066).

In addition to prospective analyses by the BARI 2D Data Safety Monitoring Board which found no evidence to require discontinuation of the use of RSG or revision of the study protocol, the BARI 2D Steering Committee also performed post-hoc analyses to evaluate the cardiovascular safety of RSG among trial participants (abstract accepted ADA 2010). These analyses are epidemiologic in nature and do not represent results from a randomized, controlled trial of RSG. Nonetheless, these analyses do provide additional data regarding the cardiovascular safety of RSG in a high-risk patient population (all patients had T2DM and established ischemic heart disease) in a study which included prospectively adjudicated cardiovascular events, included contemporary standard of care management of cardiovascular risk factors, and 5 years follow-up. The outcomes for the RSG-specific analyses included the BARI 2D primary outcome (all-cause mortality) and principal secondary outcome (MACE; composite of all-cause mortality, myocardial infarction, and stroke). Additionally, the individual outcome of myocardial infarction was included in light of hypotheses raised by meta-analyses of short-term RSG trials. Results for the main analysis of RSG versus no-TZD are shown in Figure 18.

Figure 18 BARI 2D: Results for Rosiglitazone versus no-TZD on MACE, Myocardial Infarction, and All Cause Mortality



Note that the relative risks are estimates from multivariate models that adjust for patient demographic and clinical characteristics and for the concurrent use of other diabetic drugs.

These results show no numeric or statistically significant increase in risk for RSG for all-cause mortality, MACE or myocardial infarction with point estimates less than unity and the 95% CI upper limit for each endpoint less than 1.2. These results are consistent with the primary result from RECORD showing no increase in overall CV risk. This is important because all 2,368 patients in BARI 2D have established IHD.

5.2. ACCORD

The NIH-sponsored ACCORD (Action to Control Cardiovascular Risk in Diabetes) study was a multicenter, randomized controlled trial (double 2x2 factorial design) trial involving 10,251 patients with type 2 diabetes and non-optimal levels of blood pressure or blood lipids who are at high risk for having a cardiovascular event [ACCORD, 2008]. A primary specific aim of the ACCORD trial is to determine the effect of a therapeutic strategy (intensive) that targets a HbA1c level of <6.0% compared with a strategy (standard) that targets an HbA_{1c} level of 7.0%–7.9% (expected median level, 7.5%) on the rate of major cardiovascular events. Due to excess deaths in the intensive treatment group (a difference of 54 deaths, or 3 per 1,000 participants each year, over an average of almost four years of treatment), the NHLBI terminated the intensive treatment group of this trial early (February 2008).

Like the BARI 2D trial, the ACCORD trial provides important information on the cardiovascular safety of RSG. Although ACCORD was not designed to compare medications, the investigators performed a number of analyses to examine whether

individual medications had an effect on mortality rate. The study included 10,251 patients, of whom 74% (n = 7,623) received RSG for a total of 19,202 patient-years. Rosiglitazone was prescribed in 91.2% of subjects in the intensive treatment group (n=4,677; 12,639 patient-years) and 57.5% of patients in the standard treatment group (n=2,946; 6,563 patient-years). Cox proportional hazards regression was used to determine if increased mortality risk was associated with ever being prescribed each glycemic medication after controlling for baseline participant characteristics and after adjusting for glycemia intervention. The investigators also estimated the hazard ratios for individual medications stratified by the presence and absence of a second medication.

There were no apparent differences between RSG and other agents with regard to mortality. The point estimate for the total mortality hazard ratio for RSG (compared to other anti-glycemic agents) after adjustment for baseline characteristics was below 1.0 in both the intensive and standard-treatment groups, and both the point estimates and upper bound of the 95% CI was lower for RSG than for other commonly used anti-glycemic agents (MET, SU, and insulin). When RSG use was stratified by addition of insulin, there was no significant increase in the risk of mortality with any type of insulin compared with RSG alone (any insulin, p=0.53; basal insulin, p=0.19; bolus insulin, p=0.68; premixed insulin, p=0.93).

5.3. VADT

The Veterans Affairs Diabetes Trial (VADT) was a multicenter, randomized, open-label study in 1,791 patients sponsored by the Veterans Affairs Cooperative Studies Program to evaluate the effect of intensive glycemic control on CV events in high risk patients with type 2 diabetes [Duckworth, 2009]. While patients were randomized to glycemic intervention arms, antihyperglycemic agents were nonrandomized. Patients could receive MET or glimepiride plus RSG and the addition of insulin or other oral agents to reach glycemic targets. Although the VADT study was not designed to evaluate the effect of any individual diabetes medication on outcomes, a series of analyses were conducted retrospectively to assess the potential effect of RSG therapy on cardiovascular outcomes and mortality during the trial.

Rosiglitazone was not a randomized agent and its use was likely limited in subjects at high risk of CHF, consistent with recommendations for use. In both the standard and intensive treatment arms, 95% of patients (n=1,705) received RSG and the majority of these patients (79%, n=1,408) received the maximum dose (8 mg/day) at some time during the trial. Investigators tested the hypothesis that RSG had no effect on cardiovascular mortality or morbidity using two analyses: case-control and time-dependent analyses. Events included in the analyses were (a) myocardial infarction, (b) CV death, (c) MI or CV death, and (d) new or worsening congestive heart failure (CHF). The case-control analysis showed significantly fewer patients taking RSG died from CV causes (p=0.02) or had a myocardial infarction (p=0.05) or cardiovascular death (p=0.01) compared to controls. Time-dependent covariate analysis showed no evidence of an increase in CV death (HR <0.5), myocardial infarction (HR <0.75) or cardiovascular death (HR <0.5) with RSG. All hazard ratios were less than one and statistically significant with the exception of MI, for which the HR was less than one but not significant. Investigators concluded that there was no evidence to suggest that RSG

increases the risk of cardiovascular mortality or morbidity in patients with type 2 diabetes [Moritz, 2008].

5.4. Conclusion

Even though none of the trials above were specifically designed to examine the cardiovascular safety of RSG, the three clinical trials discussed above provide important information related to RSG because the trials are of long duration (3.5 to 5.6 years), enrolled over 14,000 patients, endpoints were adjudicated, and included a large number of patients at high risk of CV disease.

In post-hoc analyses conducted by the Steering Committees of these trials, BARI 2D assessed the risk of all-cause mortality and MACE (composite of all-cause mortality, myocardial infarction, and stroke) associated with RSG, ACCORD assessed the effect of RSG on mortality rate, and VADT examined the risk of myocardial infarction, cardiovascular death, MI/CV death, and new or worsening congestive heart failure associated with RSG.

All three studies concluded that there was no evidence to suggest that RSG was associated with increased cardiovascular risk compared to other anti-glycemic agents.

6. ONGOING RESEARCH

Currently, two randomized, well controlled clinical trials are ongoing to characterize further the benefit and risk associated with RSG in the treatment of T2DM. The Bone mechanism of action (MOA) study compares RSG with MET to characterize the effects of RSG on bone mass and architecture in postmenopausal women, given the increased incidence of fracture among female patients observed in two long-term clinical studies ADOPT and RECORD. TIDE (TZD Intervention and Vitamin D Evaluation) is a post-marketing required study comparing RSG with placebo and PIO to establish definitively the ischemic safety of RSG and to provide a head-to-head comparison of RSG and PIO on CV outcomes in patients with T2DM.

The TIDE trial is a multi-center, international, randomized, double-blind, placebo-controlled, cardiovascular outcomes study. The trial is enrolling 16,000 patients with T2DM at risk for cardiovascular disease from 750 clinical centers in 40 countries. TIDE is being conducted in collaboration with Population Health Research Institute (PHRI) at McMaster University, an institution which has conducted multiple cardiovascular outcomes trials. The study co-principal investigators are Drs. Hertzel Gerstein and Salim Yusuf.

For the trial, an oversight committee provides independent monitoring of patient safety. Experts in cardiovascular disease, diabetes, and statistics comprise an Independent Data Monitoring Committee (IDMC) that meets regularly to review unblinded data, specifically data on cardiovascular outcomes, and at its most recent meeting the IDMC has not found any concerns regarding patient safety in the study (Dec 2009).

The TIDE trial is designed principally to evaluate the ischemic cardiovascular safety of RSG and secondarily to compare the effects of RSG and PIO on cardiovascular outcomes. Patients (16,000) with T2DM and risk factors for CV disease will be randomized to treatment with RSG, placebo+standard of care, or PIO for up to 5.5 years of followup for the TZD comparison. The primary outcome for TIDE is MACE (major adverse cardiovascular events; composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke). The primary endpoint in TIDE is the evaluation of the non-inferiority (margin 1.3) for RSG versus placebo on MACE. The non-inferiority margin has been agreed by FDA and is consistent with the 2008 FDA Guidance for the evaluation of cardiovascular safety of diabetes medicines. A co-primary endpoint structure has been included to allow for a superiority evaluation of the TZD class (pooled RSG and PIO group) versus placebo on MACE. The co-primary structure has been accounted for in the statistical power and sample size determination as agreed by FDA. Finally, TIDE includes, as a secondary endpoint, evaluation of non-inferiority of RSG and PIO on MACE.

Comparing RSG with PIO in the TIDE study is supported by assessing the final results from the long-term, randomized, prospective, cardiovascular outcomes trials RECORD (RSG) and PROactive (PIO). The PROactive trial [Dormandy, 2005], in a population at relatively high risk of cardiovascular events, showed that PIO was not significantly different from placebo for its primary composite cardiovascular outcome (HR 0.90, 95% CI 0.80-1.02), although congestive heart failure was not included, a known effect of the

TZD class. Results from RECORD showed that RSG was similar to commonly used treatments for diabetes (MET and SU) for its primary composite cardiovascular outcome that included congestive heart failure (HR 0.99, 95% CI 0.85-1.16). The RECORD population had fewer patients with established cardiovascular disease than PROactive, although analyses from the BARI 2D trial, conducted entirely in high-risk patients with ischemic heart disease, showed no increase in mortality or ischemic cardiovascular events associated with treatment with RSG. Therefore, given the different populations, comparators, and endpoints, it is difficult to compare the data from PROactive and RECORD. The TIDE trial will therefore provide the first opportunity for a definitve comparison of PIO and RSG.

In summary, the large sample size, long-term follow-up, randomized, controlled design, and pre-specified endpoints contribute to TIDE definitively establishing the ischemic CV safety of RSG.

7. BENEFIT RISK OF ROSIGLITAZONE

It is important to consider the benefit risk profile of RSG in the context of the unmet needs and challenges of managing patients with T2DM.

7.1. Disease Background

T2DM is a growing public health problem worldwide. The increasing incidence and prevalence of T2DM is seen in virtually all ethnic and racial groups- worldwide 171 million persons were estimated to have T2DM in 2000 with this number projected to increase to 366 million by 2030. According to the prevalence data estimates released by the Centers for Disease Control and Prevention, diabetes affects nearly 24 million people in the US, an increase of almost 3 million in approximately two years. In addition to the 24 million with diabetes, another 57 million people are estimated to have pre-diabetes, a condition that puts people at increased risk for diabetes. The epidemic of T2DM is closely associated with increasing incidence of obesity, which together with associated insulin resistance are key risk factors for the development of the disease. T2DM is characterized by hyperglycemia due to a relative insufficiency of insulin and presents a major health risk to the individual, particularly with regard to chronic risks of microvascular complications, which include eye damage leading to blindness, kidney damage leading to dialysis, and nerve damage that can affect multiple parts of the body. Macrovascular complications include stroke, myocardial infarction, and death. In most countries diabetes is among the top five causes of death, with cardiovascular (CV) disease being the most common cause of mortality in diabetic patients.

Patients with T2DM are at a 2-4 fold increased risk of macrovascular complications compared to non diabetic subjects and this is partly due to obesity, dyslipidaemia, hypertension as well as hyperglycemia. It is therefore important to have a multifactorial approach to the treatment of these patients. Epidemiological data have shown that diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction [Haffner, 1998]. Trials that included patients with diabetes and coronary heart disease have shown that cholesterol lowering with statins substantially reduced the risk of subsequent cardiovascular events. Furthermore in primary prevention studies such as the CARDS study, benefit was seen with atorvastatin even in patients without a high LDL cholesterol and supports the use of statins in the majority of patients with type 2 diabetes. The ADA and NICE Guidelines recommend that statin therapy should be added for diabetic patients over the age of 40 regardless of lipid levels.

Blood pressure control as with lipid control has clearly been shown to be important in reducing CV events. As such the ADA guidelines recommend aiming for BP <130/80 mm Hg. The impact of glucose lowering on reduction of CV events is, however, not clear. More recent studies, such as ACCORD, ADVANCE, and VADT, were designed to assess intensive vs standard glucose control [ADVANCE, 2008]. These studies did not show a difference in macrovascular events between the groups.

Although the benefit of lowering glucose to reduce macrovascular complications is not clear, there is more evidence that supports the benefit of sustained glucose lowering to

reduce microvascular complications. The UKPDS suggests that, for a 0.9% decrease in HbA1c, there is about 25% decrease in the incidence of microvascular endpoints (such as retinopathy, albuminuria and need for retinal photocoagulation) [UKPDS 33, 1998]. It is important to note that the reduction in microvascular events was not seen until after six years. In the VADT study, there was evidence of benefit in the intensive treatment group on microvascular complications with less progression to microalbuminuria than in the standard treatment group. The ADVANCE study also showed a reduction in the progression of albuminuria in the intensive treatment group compared to the standard treatment group.

7.2. Choice of oral agents for the management of type 2 diabetes

A major challenge in diabetes management is to lower glucose, without causing hypoglycemia, and to maintain glycemic control over the lifetime of the patient. As people are developing T2DM at younger ages, glycemic control needs to be maintained over several decades of life. The UKPDS study demonstrated the inexorable progression of T2DM over time despite intensive efforts to maintain near normal glycemia with a single agent. With each of the three therapies used in UKPDS (MET, SU and insulin), there was an initial reduction of glucose toward the target of normoglycemia, but over time there was a need to intensify therapy, either by the addition of another oral agent or an increase in insulin dose, due to a progressive rise in HbA1c [UKPDS 33, 1998; UKPDS 34, 1998].

Six classes of oral anti-glycemic medications with varying modes of action are currently available to patients with T2DM for reducing blood glucose. No single agent addresses the full range of pathophysiological defects characteristic of T2DM. This, coupled with the inexorable deterioration of glycemic control over time, and increasingly stringent target goals makes the availability and combination use of a range of anti-hyperglycemic agents essential. Patient variability heightens the need for different treatment options. Table 14 summarizes the expected reduction in HbA1c and side effects for the available classes of anti-glycemic agents.

Table 14 Available Agents for the Treatment of Type 2 Diabetes Mellitus

Drug Class	Route of Administration	Expected HbA1c Reduction (Monotherapy)	Side Effects
Insulin	Subcutaneous injection (inhaled, short-acting insulin recently approved)	>1.5 to 2.5% (no dose limit)	Hypogylcemia, weight gain
Sulfonylureas (SUs)	Oral	1.5%	Hypogylcemia, weight gain, probable ischemic risk with certain SUs
Biguanide/Metformin	Oral	1.5%	Rare lactic acidosis, contraindicated in patients with renal impairment
Alpha-glucosidase inhibitors	Oral	0.5 to 0.8%	GI side effects
TZDs/PPAR agonists	Oral	0.5 to 1.5%	Anemia, weight gain, edema, heart failure, fracture, cardiac ischemic risk; potential cancer risk (Bladder cancer signal with Pioglitazone
Glinides	Oral	1 to 1.5%	Hypoglycemia
Amylin analogues	Subcutaneous injection	0.5 to 1.0%	GI side effects
GLP-1 analogues*	Subcutaneous injection	0.4 to 0.8%	GI side effects
DPPIV-inhibitors**	Oral	0.5 to 0.9%	Limited clinical experience; nonclinical safety signals for many in development

*Exenatide is the only approved GLP-1 analogue.
**Sitagliptin is the only approved DPPIV-inhibitor (approved 10/06)

At present ADA and EASD guidelines recommend MET as the initial agent for diabetic treatment [Nathan, 2009]. Sulfonylureas also have been considered a mainstay of treatment since the 1950s. Consequently, MET and SU are the most commonly prescribed diabetes agents.

There are limitations to these commonly prescribed diabetes agents. The treatment limitations of MET are gastrointestinal (GI) side effects and the risk of lactic acidosis. The latter adverse event is rare (0.03 per 1000 patient years), though life threatening. The

risk of lactic acidosis is increased in conditions associated with acidosis such as renal, hepatic, and cardiac impairment and chronic hypoxemia. The GI effects of nausea, diarrhea and vomiting occur in 5-30% of MET treated subjects with resultant discontinuation of treatment in about 3-4% of subjects [Davidson, 1997; Kahn, 2006]. Additionally about 10% of subjects cannot tolerate MET at any dose due to GI side effects [Krentz, 2005].

The main risk with SUs is hypoglycemia which can limit the ability to achieve therapeutic goals. Mildly symptomatic hypoglycemia was reported by 20% of SU treated patients in UKPDS annually. The annual incidence of severe hypoglycemia, which may result in significant morbidity as well as mortality, has been recorded in 1% of the SU treated patients. SUs are associated with weight gain and short lived glycemic control.

Another limitation of MET and SU is that neither agent, as monotherapy, can maintain glycemic control as the disease progresses. Therefore, there is a need for further add on therapy.

Metformin is the only anti-hyperglycemic treatment to have shown some benefits on CV complications, in a subgroup analysis of obese patients in UKPDS [UKPDS 34, 1998]. There was no evidence that intensive treatment with chlorpropamide, glibenclamide, or insulin had a specific adverse effect on macrovascular disease. Both TZD's have CV outcome data (RECORD and PROactive), which do not show an increase in CV events. There are no CV outcome data with DPPIV or GLP-1 analogues.

7.3. Benefits of Rosiglitazone

In the short-term, RSG significantly reduces HbA1c by 1-1.5% and has been shown to be effective in a wide range of patients from those patients newly diagnosed to patients with advanced disease treated with combination therapy. Rosiglitazone has been studied in various patient types including elderly, renally impaired, various ethnicities, those with known heart failure, or with known cardiovascular disease. In the long-term, ADOPT demonstrated that glycemic control with RSG was more durable than that with MET or glyburide in newly diagnosed T2DM patients. Mean HbA1c was maintained at <7% for 54 months for RSG compared to 45 months for MET and 32 months for glyburide. The glycemic control observed in the RECORD study is consistent with the results from ADOPT. This durability of glycemic control in two long-term studies reflects RSG's favorable impact on the underlying pathophysiological defects of T2DM, insulin resistance and beta cell dysfunction.

Other than UKPDS, which looked at first generation SU, insulin and MET, RECORD and ADOPT provide the longest glycemic data, as these studies were up to 6 years in duration. The longest duration data on PIO (three years) comes from PROactive, and there are no long-term controlled studies beyond two years on any of the DPPIVs or GLP-1s.

The UKPDS and DCCT studies demonstrated that improved glycemic control was associated with improvements in urinary albumin excretion and reduced progression to nephropathy. In the ADOPT study, RSG demonstrated a reduction in albumin creatinine ratio. In the RECORD study, there was also a reduction in the albumin creatinine ratio

with RSG therapy, as well as less progression of albuminuria compared to the control group of MET/SU. As demonstrated in UKPDS, intensive glycemic control over the long-term is associated with a reduction in microvascular complications. In RECORD, the risk of diabetes related eye or foot events with RSG was similar to MET/SU, which have already demonstrated reductions in microvascular events from the UKPDS study. There are limited or no published long-term microvascular data with PIO, DPPIVs or GLP-1s.

Hypoglycemia is a concern for patients with T2DM as they strive to improve glycemic control. RSG and MET, as monotherapies, are not associated with hypoglycemia. Therefore, there is minimal risk when RSG is used in combination with MET. However when RSG is used with SU or insulin, there should be consideration for dose reductions with the SU or insulin to reduce the risk of developing hypoglycemia.

7.4. Risks of Rosiglitazone

RSG, like other TZDs alone or in combination with other anti-hyperglycemic agents, is associated with dose related fluid retention, which, in susceptible subjects, can lead to edema and symptoms of CHF. This has been well described and, therefore, TZDs are not recommended in patients with symptomatic heart failure. If patients develop signs or symptoms of heart failure, this should be managed according to current guidelines with consideration of adding in diuretics or reducing the dose or withdrawing RSG.

RSG treatment, like other TZDs, has been associated with an increase in weight. The mechanism of weight gain is unclear, but probably involves a combination of fluid retention and fat accumulation. The fat volume is predominantly peripheral, in non-abdominal sites, with no increase in intra-abdominal visceral adiposity. Insulin and SU are also associated with weight gain related to improved glucose control.

Bone mineral density (BMD) is increased in patients with T2DM compared with non-diabetics [Vestergaard, 2007]. Despite this increase in BMD, there have been accumulating data to indicate that patients with T2DM are at increased risk of non-vertebral fracture [Bonds, 2006; Nicodemus, 2001; Vestergaard, 2005], particularly fractures of the hip, arm and foot. In long-term studies, both TZD's have demonstrated an increase in the incidence of fracture rates, predominantly in women. The majority of fractures in patients who received RSG were in the upper arm (humerus), hand, or foot, sites that are different from those associated with post menopausal osteoporosis (e.g., hip or spine).

7.5. Comparative Considerations

RSG has an established efficacy and tolerability profile with an absence of hypoglycemia and lack of gastrointestinal intolerability. RSG can be used in a wide range of patients in whom other agents may not be suitable due to lack of tolerability or contraindication. Benefit risk consideration may favor the use of RSG in some elderly patients who are at particular risk of serious consequences of hypoglycemia with SUs. Metformin, though extremely useful, is also limited due to contraindication in renally impaired patients and, in some patients, poor gastrointestinal tolerability. In patients unable to achieve or maintain adequate glycemic control on their current therapy, due to its complementary

mode of action, RSG has been shown to provide additional benefits. Although other agents have recently become available (i.e., DPPIVs or GLP-1s), they have limited long-term efficacy and safety data. There are no long-term durable glycemic control data, no data on microvascular complications and no data on CV outcomes with either the DPPIVs or GLP-1s.

There are no large long-term head-to-head studies comparing RSG to PIO. Both agents have demonstrated short term glycemic control. RSG has more long-term durable glycemic control data (up to four to five years of data from both ADOPT and RECORD) compared to three years from PROactive. Both PIO and RSG cause weight gain, fluid retention and worsening CHF and are associated with an increased risk of fractures.

A short term, 6-month, head-to-head study suggested modest differences in lipids [Goldberg, 2005]. Because diabetics should be treated with lipid-lowering therapy as part of standard of care, a more relevant study would compare RSG vs PIO combined with statin therapy. In a study that evaluated the addition of simvastatin to TZD therapy, patient lipid profiles improved regardless of which TZD was taken. There was no significant difference in mean percentage change in LDL-c between RSG and PIO, following the addition of simvastatin.

There are extensive long-term data showing no increased carcinogencity risk with RSG. Comparable long-term data assessing the carcinogenicity risk with other anti-glycemic agents, including PIO, DDPIVs, and GLP-1s are not currently available.

The availability of long-term studies on RSG has allowed an evaluation of its impact on microvascular complications. RECORD showed no increase in SAEs of microvascular events compared to MET and SU. There are no long-term published data on microvascular complications on PIO.

There have been two large prospective cardiovascular studies, PROactive and RECORD. It is difficult to compare these two studies because of different patient populations (RECORD moderate CV risk patients, PROactive high CV risk patients); different comparators (RSG vs active comparators and PIO vs placebo); and different definitions of the primary endpoints (RECORD included CHF and PROactive did not). There have been several large epidemiological and observational studies which have compared RSG and PIO with inconsistent results. There is no completed large head-to-head randomized clinical trial comparing RSG and PIO. Therefore, the current evidence does not permit a conclusion that there is a difference in macrovascular complicatons between RSG and PIO.

A recent Science Advisory from the American Heart Association and American College of Cardiology Foundation entitled “Thiazolidinedione Drugs and Cardiovascular Risks” summarized the available data concerning TZDs and cardiovascular risk, with a focus on ischemic heart disease (IHD) events. It concluded that there is no reliable evidence to support the choice between RSG and PIO [Kaul, 2010].

7.6. Overall Conclusions

Rosiglitazone is an option for treatment for patients with type 2 diabetes mellitus. Rosiglitazone has been extensively studied and has demonstrated glycemic efficacy, both in the short-term, with up to 1.5% reduction in HbA1c, and in the long-term showing durable glycemic control compared to MET and SU. Short- and long-term reductions in microalbuminuria have been demonstrated with RSG treatment. In RECORD, there was no increase in microvascular complications compared to MET and SU, agents that have demonstrated reductions in microvascular events in the UKPDS study. There is now a large body of long-term data on the CV safety of RSG. The totality of the evidence, from RECORD and other long-term studies, demonstrate no increase in the overall risk of CV morbidity and mortality compared to MET or SU. The safety concerns of RSG have been well characterized (weight gain, fluid retention, edema, CHF, and fractures) and with appropriate labeling and advice are clinically manageable, collectively and individually. Given the appropriate management of risks, coupled with long-term glycemic control achieved with RSG and reassuring data on CV safety, RSG is an important option for the treatment of type 2 diabetes with a favorable benefit risk in both women and men.

8. REFERENCES

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9. APPENDICES

9.1. Appendix 1. Minutes of July 2007 Joint Advisory Committee Meeting

Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland

Summary Minutes of the joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on July 30, 2007.

On July 30, 2007 the committee discussed Cardiovascular ischemic/thrombotic risks of the thiazolidinediones, with focus on rosiglitazone, as presented by the FDA and GlaxoSmithKline.

These summary minutes for the July 30, 2007 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee were approved on Tuesday, August 1, 2007.

I certify that I attended the July 30, 2007 joint meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committee and that these minutes accurately reflect what transpired.

_____//S//_____	_____	_____//S//_____	_____
Cathy A. Miller, M.P.H., R.N.	Date	Clifford J. Rosen, M .D.	Date
Designated Federal Official		(Acting) Chair	

FINAL MINUTES
Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
July 30, 2007

A verbatim transcript will be available in approximately 4-6 weeks from the date of the meeting, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder07.htm#EndocrinologicMetabolic

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 30, 2008 at the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and the sponsor (GlaxoSmithKline). The meeting was called to order by Clifford J. Rosen, M.D (Acting Committee Chair); the conflict of interest statement was read into the record by Cathy A. Miller, M.P.H. (Designated Federal Official). There were approximately 450 persons in attendance. There were 16 speakers for the Open Public Hearing session.

Issue: Cardiovascular ischemic/thrombotic risks of the thiazolidinediones, with focus on rosiglitazone, as presented by the FDA and GlaxoSmithKline.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting): Kenneth D. Burman; M.D.; Jessica W. Henderson, Ph.D.; Katherine M. Flegal, Ph.D.; Clifford J. Rosen, M.D.;

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Sean Hennessy, Pharm.D, Ph.D.; Judith M. Kramer, M.D., M.S.; Timothy S. Lesar, Pharm.D.;

Special Government Employee Consultants (Voting): Ruth S. Day, Ph.D.; Judith Fradkin, M.D.; Nancy L. Geller, Ph.D.; Allison Goldfine, M.D.; Eric S. Holmboe, M.D., F.A.C.P.; Rebecca Killion (Patient Representative); Arthur A. Levin, M.P.H.; Arthur J. Moss, M.D. [participating via teleconference]; Lewis S. Nelson, M.D., F.A.C.E.P.; David Oakes, PhD. [participating via teleconference]; Thomas G. Pickering, M.D., D.Phil.; Peter J. Savage, M.D.; David S. Schade, M.D.; Morris Schambelan, M.D.; John R. Teerlink, M.D.; Gerald van Belle, Ph.D.

Special Government Employee Consultants (Non-Voting): Curt D. Furberg, M.D., Ph.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Non-Voting):
Steven W. Ryder, M.D. (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members Present (Non-Voting):
Annette Stemhagen, Dr.Ph. (Industry Representative)

Guest Speakers (Non-Voting): David Gordon, M.D., Ph.D., M.P.H.; Robert E. Ratner, M.D.

Consultants (Non-Voting): Steven Nissen, M.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present: Nelson B. Watts, M.D. (Chair); Sonia Caprio, M.D.; Michael A. Proschan, Ph.D.

Drug Safety and Risk Management Advisory Committee Members Not Present: Richard Platt, M.D., M.Sc.; Terry C. Davis, Ph.D.; Susan R. Heckbert, M.D., Ph.D.

FDA Participants (Non-Voting): Douglas C. Throckmorton, M.D.; Sandra L. Kweder, M.D.; Robert J. Meyer, M.D.; Mary H. Parks, M.D.; Gerald Dal Pan, M.D., M.H.S.; Mark I. Avigan, M.D., C.M.; Robert T. O'Neill, Ph.D.

Designated Federal Official: Cathy A. Miller, M.P.H., R.N.

FINAL MINUTES
Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
July 30, 2007

Open Public Hearing Speakers:
Sidney M. Wolfe, M.D., Director, Public Citizen's Health Research Group; J. Rick Turner, Ph.D., P.G.C.E., Campbell University School of Pharmacy; George A. Diamond, M.D., F.A.C.C.; Sanjay Kaul, M.D., F.A.C.C., Cedar-Sinai Medical Center Division of Cardiology; Richard Hellman, M.D., F.A.C.P., F.A.C.E., President, American Association of Clinical Endocrinologists; Jerome V. Tolbert, M.D., Ph.D.; Eileen Rivera Ley, Director, Diabetes Initiatives, Diabetes Action Network, National Federation of the Blind; Gail Brashers-Krug, Voice of Diabetic and Diabetes Action Network; Bruce Trippe, M.D., F.A.C.E., Endocrinology Associates of Montgomery; Raul Fernandes; Richard E. Ralston, Executive Director, Americans for Free Choice Medicine; Cahrles E. Steele; Farhad Zangeneh, M.D., F.A.C.P., F.A.C.E., Endocrine, Diabetes and Osteoporosis (EDOC); Jamie Davidson, M.D., Endocrinologist; Michael R. Peterson, D.V.M., M.P.H./Thomas Bacon, Pharm.D.

The agenda was as follows:

Call to Order and Introductions	**Clifford J. Rosen, M.D.** (Acting) Committee Chair
Conflict of Interest Statement	**LCDR Cathy A. Miller, M.P.H.** Designated Federal Official Endocrinologic and Metabolic Drugs Advisory Committee
Introduction/Background	**Mary H. Parks, M.D.** Director, Division of Metabolism and Endocrine Products, CDER, FDA

PRESENTATIONS:

Guest Speaker Presentation:

Achieving Diabetes Targets: Where Are We and How Can We Do Better?	**Robert E. Ratner, M.D.** Vice-President of Scientific Affairs MedStar Research Institute Washington, DC

GlaxoSmithKline Presentations:

. Introduction	**Ronald L. Krall, M.D.** Senior Vice President and Medical Officer GlaxoSmithKline
Review of Data	**Murray W. Stewart, D.M., FRCP** Vice President, Clinical Development GlaxoSmithKline
Conclusions	**Ronald L. Krall, M.D.**
	Clarifying Questions from the Committee
	Break

FDA Presentations:

FDA Meta-Analysis	**Joy D. Mele, M.S**. Statistician, FDA/CDER Office of Biostatistics, Division of Biometrics II
Overview of Large, Long-Term,	**Karen M. Mahoney, M.D.**

Prospective Trials of Thiazolidinediones	Medical Officer, FDA/CDER Division of Metabolism Endocrine Products
NIH Speaker Presentation:	
Use of Rosiglitazone in the BARI 2D Trial	**David J. Gordon, M.D., Ph.D.** Division of Cardiovascular Diseases National Institute of Health (NIH) National Heart, Lung and Blood Institute
FDA Presentations (Continued):	
Observational Studies: Effect of Anti-Diabetic Agent Choice on Cardiovascular Morbidity and Mortality in Type II Diabetes Mellitus	**Kate Gelperin, M.D., M.P.H.** Medical Officer, FDA/CDER Office of Surveillance and Epidemiology, Division of Drug Risk Evaluation
Assessment of health risks and Benefits associated with rosiglitazone	**David Graham, M.D., M.P.H.** Associate Director, FDA/CDER Associate Director for Science and Medicine, Office Surveillance and Epidemiology
Conclusions and Summary	**Robert Meyer, M.D.** Director, FDA/CDER Office of New Drug Evaluation II
	Gerald Dal Pan, M.D., M.H.S. Director, FDA/CDER Office of Surveillance and Epidemiology
	Lunch
	Open Public Hearing
.	**Questions to the FDA/Discussion**
	Break
`	**Questions to the Committee**
	Adjourn

Questions to the Committee:

1. Please comment on the contribution of the meta-analysis of the 42 controlled clinical trials (e.g., strengths and limitations) to the understanding of cardiac ischemic risk for Avandia.

- ***Most of the committee members agreed that there was at least a strong signal for increased cardiac ischemic risk, though concerns were raised about the short duration of the trials; the quality of the data; low number of cardiac events; lack of cardiac eventadjudication; and concerns about the heterogeneity of the study population.***
- ***The committee further identified subpopulations at potential risk, such as nitrate users, those with established cardiovascular disease and those with coexistent insulin therapy, who appeared to have an increased risk.***
- ***The committee pointed out that the outcome of interest in these trials, at the time they were designed and conducted, was not ischemic cardiac events, making the study data difficult to***

interpret, though they raise awareness of a strong signal; adverse events in the 42 trials were not collected in a standardized, prespecified or adjudicated in an ongoing way

- ***The committee requested that the FDA have more rigorous requirements for clinical trials to assure the follow-up of subjects who withdraw from assigned treatment, even for trials based on short-term data, with reporting of all adverse events.***

(See transcript for detailed discussion)

2. Please comment on the contribution of the observational cohort studies (e.g., strengths and limitations) to the understanding of cardiac ischemic risk for Avandia.

- ***There was considerable discussion from the committee on the observational studies and their potential value. Some on the committee stated that the observational studies are helpful in capturing what is actually happening in practice and getting a sense of population risk.***
- ***While some of the committee members commented that the observational studies were high quality and carefully done, they also raised concerns about biases, difficulty interpreting the data for users [treated] versus non-users [not-treated].***
- ***The committee cautioned that observational studies have in the past, yielded conflicting results from those of randomized clinical trials (e.g. hormone replacement therapy), therefore there is limited weight we can place on these studies***
- ***The committee emphasized the importance that we are not comparing this drug to placebo since diabetics need to take something to control their disease***
- ***The committee commented that the data may suggest that the difference between the two TZDs [rosiglitazone and pioglitazone] may not be as great as claims that have been made based on information obtained from the observational studies***
- ***Some of the committee suggested that if the randomized controlled trials will not give us the answers we need, we are left with information that can be obtained from well designed observational studies, along with a registries approach, to capture out of hospital events***

(See transcript for detailed discussion)

3. Please comment on the contribution of large randomized controlled trials of rosiglitazone (e.g., strengths and limitations of DREAM, ADOPT, and RECORD) to the understanding of cardiac ischemic risk for Avandia.

- ***The committee commented that given the real world setting for treatment of diabetes is no longer no treatment versus drug, caution should be taken about discarding studies with a very practical clinical design like RECORD, given the hard adjudicated endpoint; however, there are concerns about DREAM and ADOPT, given the inclusion of non-diabetic or new diabetic patients in the studies; the risk in these two studies is very different***
- ***The committee expressed concern and disappointment that these studies will have the 'power' to negate whether there is potentially a significant increase in risk. The committee also expressed its concern that these trials do not study the patients of interest, and in fact, excluded the patients that we are concerned about; therefore lack of a signal for the outcomes in these trials may not necessarily inform decisions regarding risk for Avandia..***
- ***Though there is evidence of increased CVD risks with Avandia, the committee identified the need for more long-term data and within sub-groups, particularly patients taking insulin+rosiglitazone; patients with congestive heart failure and those taking nitrates; and the elderly population.***

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- ***The committee commented that the FDA is in a position to make a greater demand, in terms of accumulating more endpoints, specifically in RECORD, and even expanding the number of patients.***
- ***The committee added that, while there is value in all the varied types of studies [meta-analysis, observational studies and long-term trials], there needs to be a model to evaluate the conclusions of all of these studies.***
- ***The committee members expressed an interest in additional analyses that would evaluate all relevant cardiovascular endpoints occurring to a subject in the trial, and not limiting analyses simply to the 'time to first event', especially for longer term clinical studies of several years duration.***

(See transcript for detailed discussion)

4. Do the available data support a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes mellitus **(VOTE requested)?**
    - If yes, is there evidence that this risk is greater than other available therapies for the treatment of type 2 diabetes mellitus?

YES: 20 NO: 3

- ***Many of the committee members expressed their reluctance to draw conclusions comparing risk level of Avandia versus other available therapies, until additional data has been reviewed (e.g. Takeda study of pioglitazone)***
- ***Some of the committee voting 'YES' qualified their vote by adding that current data could be categorized as 'suggestive of' rather than 'evidence of' an increased cardiac ischemic risk with Avandia.***
- ***Many of the committee members qualified their 'YES' answer to the question of greater risk with Avandia, by identifying subgroups at increased risk, noting the limitations of comparison to placebo, and noting the increased risk in patients taking insulin. The committee added the need to emphasize the risks of other therapies such as sulfonylureas. The committee further commented on its concern about the lack of a dose-response relationship exhibited in the studies.***

(See transcript for detailed discussion)

5. Does the overall risk-benefit profile of Avandia support its continued marketing in the US **(VOTE requested)?**
    - If yes, please comment on what FDA should do to maximize the risk-benefit considerations (e.g., limit to certain patients, incorporate a boxed warning….)

YES: 22 NO: 1

- ***Some of the committee felt that the removal of Avandia from the market would be a draconian measure based on the current information available, emphazing the necessity of having a TZD drug available, as an option to treat diabetes***
- ***Most of the committee provided recommendations for labeling changes regarding ischemic risks. Recommendations included a black box warning for use in patients with heart failure;***

a contraindication for use with insulin though a few of the committee participants suggested a removal of the indication rather than contraindication; a warning about the use with anti-anginals (e.g. ARBs); monitoring and patient education; and perhaps a statement about ongoing research in progress. A few of the committee members suggested a black box warning for all severe congestive heart failure, concomitant insulin use, and severe arterioscleratic heart disease and use of nitrates

- ***A few committee participants expressed caution in recommending labeling changes for contraindications in certain subgroups and would also not recommend black box warning but would add warning regarding cardiovascular risks to the text of labeling.***
- ***Concerns were also raised that there is not enough emphasis on addressing the risk management issues, specifically as underrepresented in the sponsor's Risk Management Plan identified in the background for this meeting. Committee comments regarding maximizing risk-benefit considerations include those mentioned in earlier discussion such as patient registries, a reevaluation of the sponsor Risk Management Plan, and more comprehensive clinician education, citing past observations identified after the distribution of "Dear Healthcare Professional" letters.***

The committee adjourned at approximately 5:45 p.m.

(See transcript for detailed discussion)

9.2. Appendix 2. US Prescribing Information for AVANDIA

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AVANDIA safely and effectively. See full prescribing information for AVANDIA.

AVANDIA® (rosiglitazone maleate) Tablets
Initial U.S. Approval: 1999

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA
See full prescribing information for complete boxed warning.
● Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.
● AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)
● A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. (5.2)

----------INDICATIONS AND USAGE----------
AVANDIA is a thiazolidinedione antidiabetic agent indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)
Important Limitations of Use:
- AVANDIA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. (1.2)
- Coadministration of AVANDIA and insulin is not recommended. (1.2, 5.3)
- Use of AVANDIA with nitrates is not recommended. (1.2, 5.2)

---------- DOSAGE AND ADMINISTRATION----------
- Start at 4 mg daily in single or divided doses; do not exceed 8 mg daily. (2)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2)
- Do not initiate AVANDIA if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.4)

---------- DOSAGE FORMS AND STRENGTHS----------
Pentagonal, film-coated tablets in the following strengths:
- 2 mg, 4 mg, and 8 mg (3)

----------CONTRAINDICATIONS ----------
Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4)

----------WARNINGS AND PRECAUTIONS ----------
- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. (5.1, 5.3)
- Increased risk of myocardial ischemic events has been observed in a meta-analysis of 42 clinical trials (incidence rate 2% versus 1.5%). (5.2)
- Use of AVANDIA with nitrates is not recommended. (1.2, 5.2)
- Coadministration of AVANDIA and insulin is not recommended. (1.2, 5.3)
- Dose-related edema (5.4), weight gain (5.5), and anemia (5.9) may occur.
- Macular edema has been reported. (5.7)
- Increased incidence of bone fracture in female patients. (5.8)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with AVANDIA or any other oral antidiabetic drug. (5.2)

----------ADVERSE REACTIONS ----------
Common adverse reactions (>5%) reported in clinical trials without regard to causality were upper respiratory tract infection, injury, and headache. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------
Inhibitors of CYP2C8 (e.g., gemfibrozil) may increase rosiglitazone levels; inducers of CYP2C8 (e.g., rifampin) may decrease rosiglitazone levels. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: February 2009
AVD:28PI

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FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions (5.1)]*. After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.
- AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. *[See Contraindications (4) and Warnings and Precautions (5.1).]*
- A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. *[See Warnings and Precautions (5.2).]*

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

AVANDIA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

1.2 Important Limitations of Use

- Due to its mechanism of action, AVANDIA is active only in the presence of endogenous insulin. Therefore, AVANDIA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- The coadministration of AVANDIA and insulin is not recommended.
- The use of AVANDIA with nitrates is not recommended.

2 DOSAGE AND ADMINISTRATION

The management of antidiabetic therapy should be individualized. All patients should start AVANDIA at the lowest recommended dose. Further increases in the dose of AVANDIA should be accompanied by careful monitoring for adverse events related to fluid retention *[see Boxed Warning and Warnings and Precautions (5.1)]*.

AVANDIA may be administered at a starting dose of 4 mg either as a single daily dose or in 2 divided doses. For patients who respond inadequately following 8 to 12 weeks of treatment,

as determined by reduction in fasting plasma glucose (FPG), the dose may be increased to 8 mg daily as monotherapy or in combination with metformin, sulfonylurea, or sulfonylurea plus metformin. Reductions in glycemic parameters by dose and regimen are described under *Clinical Studies (14.1).* AVANDIA may be taken with or without food.

The total daily dose of AVANDIA should not exceed 8 mg.

2.1 Monotherapy

The usual starting dose of AVANDIA is 4 mg administered either as a single dose once daily or in divided doses twice daily. In clinical trials, the 4-mg twice-daily regimen resulted in the greatest reduction in FPG and hemoglobin A1c (HbA1c).

2.2 Combination With Sulfonylurea or Metformin

When AVANDIA is added to existing therapy, the current dose(s) of the agent(s) can be continued upon initiation of therapy with AVANDIA.

Sulfonylurea: When used in combination with sulfonylurea, the usual starting dose of AVANDIA is 4 mg administered as either a single dose once daily or in divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: The usual starting dose of AVANDIA in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with AVANDIA.

2.3 Combination With Sulfonylurea Plus Metformin

The usual starting dose of AVANDIA in combination with a sulfonylurea plus metformin is 4 mg administered as either a single dose once daily or divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

2.4 Specific Patient Populations

Renal Impairment: No dosage adjustment is necessary when AVANDIA is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and AVANDIA is also contraindicated in patients with renal impairment.

Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment with AVANDIA. Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy). After initiation of AVANDIA, liver enzymes should be monitored periodically per the clinical judgment of the healthcare professional. *[See Warnings and Precautions (5.6) and Clinical Pharmacology (12.3).]*

Pediatric: Data are insufficient to recommend pediatric use of AVANDIA *[see Use in Specific Populations (8.4)]*.

3 DOSAGE FORMS AND STRENGTHS

Pentagonal film-coated TILTAB® tablet contains rosiglitazone as the maleate as follows:

- 2 mg - pink, debossed with SB on one side and 2 on the other

- 4 mg - orange, debossed with SB on one side and 4 on the other
- 8 mg - red-brown, debossed with SB on one side and 8 on the other

4 CONTRAINDICATIONS

Initiation of AVANDIA in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated *[see Boxed Warning]*.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Failure

AVANDIA, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered *[see Boxed Warning]*.

Patients with congestive heart failure (CHF) NYHA Class I and II treated with AVANDIA have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic study was conducted in 224 patients with type 2 diabetes mellitus and NYHA Class I or II CHF (ejection fraction ≤45%) on background antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of fluid-related events (including congestive heart failure) and cardiovascular hospitalizations according to predefined criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed following treatment with AVANDIA compared to placebo during the 52-week study. (See Table 1.)

Table 1. Emergent Cardiovascular Adverse Events in Patients With Congestive Heart Failure (NYHA Class I and II) Treated With AVANDIA or Placebo (in Addition to Background Antidiabetic and CHF Therapy)

Events	AVANDIA	Placebo
	N = 110 n (%)	N = 114 n (%)
Adjudicated		
Cardiovascular deaths	5 (5%)	4 (4%)
CHF worsening – with overnight hospitalization – without overnight hospitalization	7 (6%) 5 (5%) 2 (2%)	4 (4%) 4 (4%) 0 (0%)
New or worsening edema	28 (25%)	10 (9%)
New or worsening dyspnea	29 (26%)	19 (17%)
Increases in CHF medication	36 (33%)	20 (18%)
Cardiovascular hospitalization*	21 (19%)	15 (13%)
Investigator-reported, non-adjudicated		
Ischemic adverse events – Myocardial infarction – Angina	10 (9%) 5 (5%) 6 (5%)	5 (4%) 2 (2%) 3 (3%)

* Includes hospitalization for any cardiovascular reason.

Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. AVANDIA is not recommended in patients with symptomatic heart failure. *[See Boxed Warning.]*

Patients experiencing acute coronary syndromes have not been studied in controlled clinical trials. In view of the potential for development of heart failure in patients having an acute coronary event, initiation of AVANDIA is not recommended for patients experiencing an acute coronary event, and discontinuation of AVANDIA during this acute phase should be considered.

Patients with NYHA Class III and IV cardiac status (with or without CHF) have not been studied in controlled clinical trials. AVANDIA is not recommended in patients with NYHA Class III and IV cardiac status.

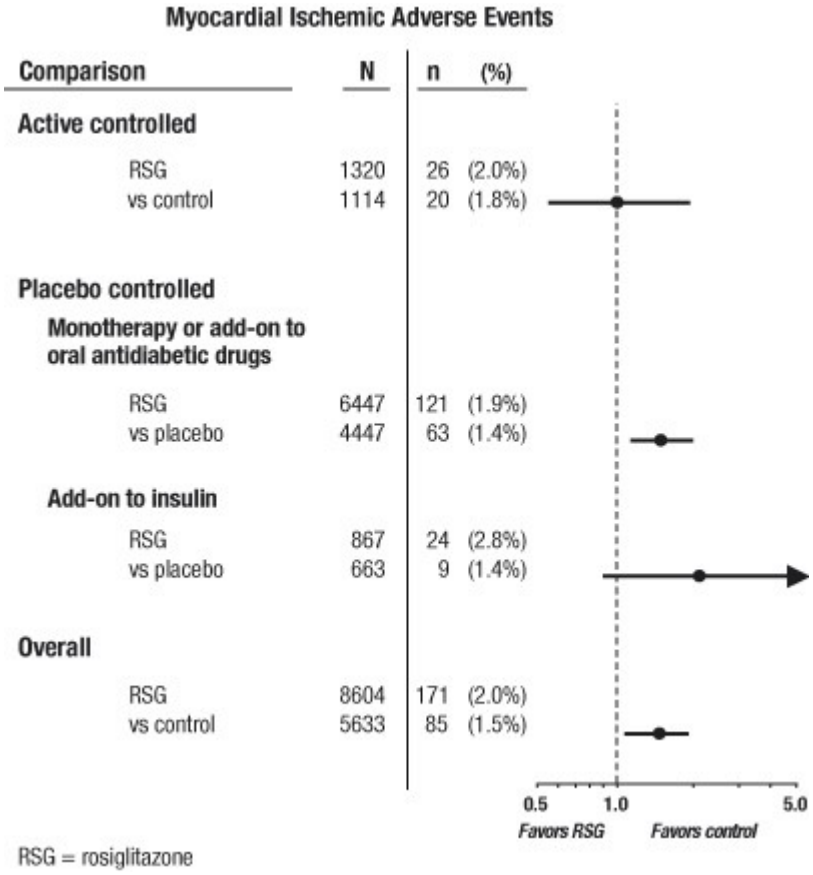
5.2 Myocardial Ischemia

Meta-Analysis of Myocardial Ischemia in a Group of 42 Clinical Trials: A meta-analysis was conducted retrospectively to assess cardiovascular adverse events reported across 42 double-blind, randomized, controlled clinical trials (mean duration 6 months).[1] These studies had been conducted to assess glucose-lowering efficacy in type 2 diabetes, and prospectively

planned adjudication of cardiovascular events had not occurred in the trials. Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls. Placebo-controlled studies included monotherapy trials (monotherapy with AVANDIA versus placebo monotherapy) and add-on trials (AVANDIA or placebo, added to sulfonylurea, metformin, or insulin). Active control studies included monotherapy trials (monotherapy with AVANDIA versus sulfonylurea or metformin monotherapy) and add-on trials (AVANDIA plus sulfonylurea or AVANDIA plus metformin, versus sulfonylurea plus metformin). A total of 14,237 patients were included (8,604 in treatment groups containing AVANDIA, 5,633 in comparator groups), with 4,143 patient-years of exposure to AVANDIA and 2,675 patient-years of exposure to comparator. Myocardial ischemic events included angina pectoris, angina pectoris aggravated, unstable angina, cardiac arrest, chest pain, coronary artery occlusion, dyspnea, myocardial infarction, coronary thrombosis, myocardial ischemia, coronary artery disease, and coronary artery disorder. In this analysis, an increased risk of myocardial ischemia with AVANDIA versus pooled comparators was observed (2% AVANDIA versus 1.5% comparators, odds ratio 1.4, 95% confidence interval [CI] 1.1, 1.8). An increased risk of myocardial ischemic events with AVANDIA was observed in the placebo-controlled studies, but not in the active-controlled studies. (See Figure 1.)

A greater increased risk of myocardial ischemic events was observed in studies where AVANDIA was added to insulin (2.8% for AVANDIA plus insulin versus 1.4% for placebo plus insulin, [OR 2.1, 95% CI 0.9, 5.1]). This increased risk reflects a difference of 3 events per 100 patient-years (95% CI -0.1, 6.3) between treatment groups. *[See Warnings and Precautions (5.3).]*

Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for Myocardial Ischemic Events in the Meta-Analysis of 42 Clinical Trials



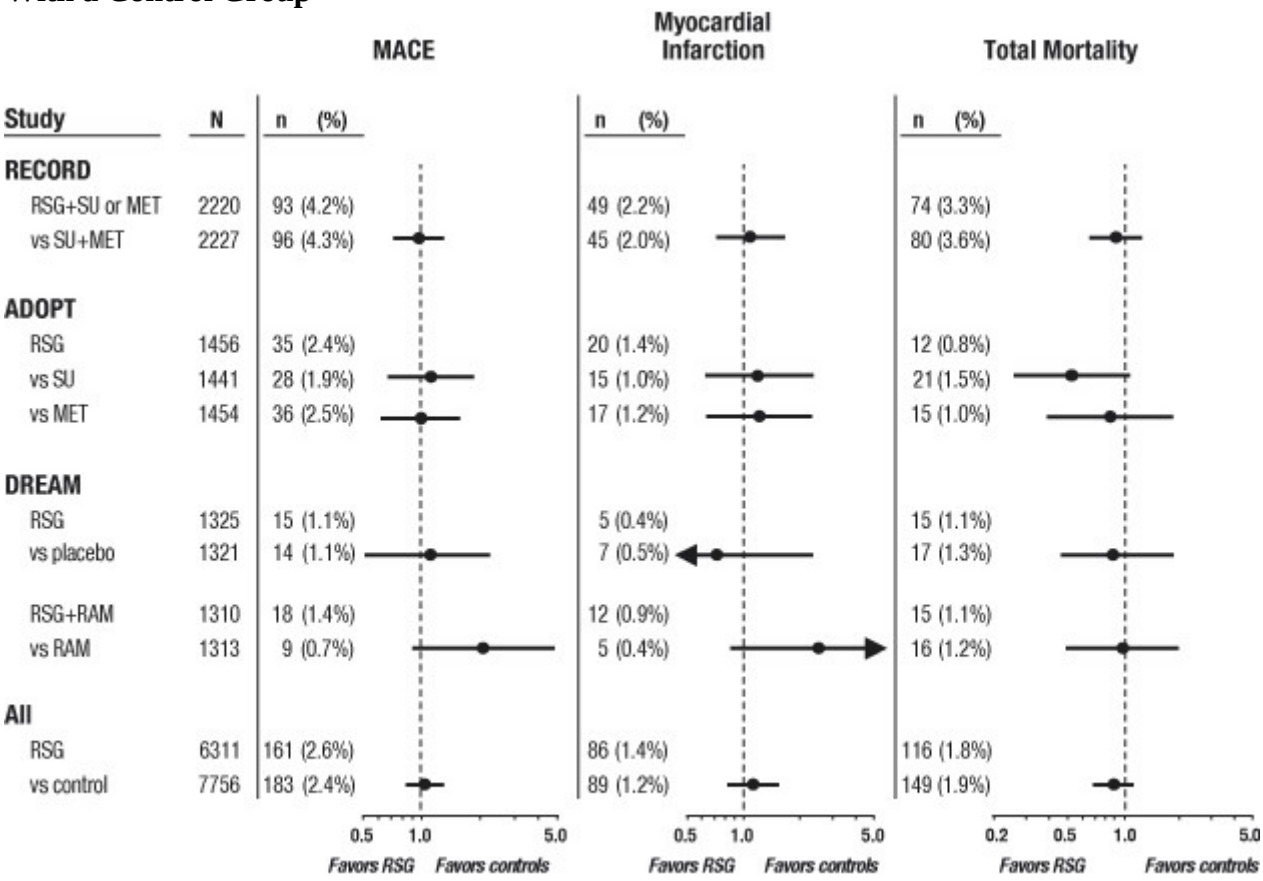
A greater increased risk of myocardial ischemia was also observed in patients who received AVANDIA and background nitrate therapy. For AVANDIA (N = 361) versus control (N = 244) in nitrate users, the odds ratio was 2.9 (95% CI 1.4, 5.9), while for non-nitrate users (about 14,000 patients total), the odds ratio was 1.3 (95% CI 0.9, 1.7). This increased risk represents a difference of 12 myocardial ischemic events per 100 patient-years (95% CI 3.3, 21.4). Most of the nitrate users had established coronary heart disease. Among patients with known coronary heart disease who were not on nitrate therapy, an increased risk of myocardial ischemic events for AVANDIA versus comparator was not demonstrated.

Myocardial Ischemic Events in Large, Long-Term, Prospective, Randomized, Controlled Trials of AVANDIA: Data from 3 other large, long-term, prospective, randomized, controlled clinical trials of AVANDIA were assessed separately from the meta-analysis. These 3 trials include a total of 14,067 patients (treatment groups containing AVANDIA N = 6,311, comparator groups N = 7,756), with patient-year exposure of 21,803 patient-years for AVANDIA and 25,998 patient-years for comparator. Duration of follow-up exceeded 3 years in each study. ADOPT (A Diabetes Outcomes Progression Trial) was a 4- to 6-year randomized, active-controlled study in recently diagnosed patients with type 2 diabetes naïve to drug therapy.

It was an efficacy and general safety trial that was designed to examine the durability of AVANDIA as monotherapy (N = 1,456) for glycemic control in type 2 diabetes, with comparator arms of sulfonylurea monotherapy (N = 1,441) and metformin monotherapy (N = 1,454). DREAM (Diabetes Reduction Assessment with Rosiglitazone and Ramipril Medication, published report[2]) was a 3- to 5-year randomized, placebo-controlled study in patients with impaired glucose tolerance and/or impaired fasting glucose. It had a 2x2 factorial design, intended to evaluate the effect of AVANDIA, and separately of ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on progression to overt diabetes. In DREAM, 2,635 patients were in treatment groups containing AVANDIA, and 2,634 were in treatment groups not containing AVANDIA. Interim results have been published[3] for RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes), an ongoing open-label, 6-year cardiovascular outcomes study in patients with type 2 diabetes with an average treatment duration of 3.75 years. RECORD includes patients who have failed metformin or sulfonylurea monotherapy; those who have failed metformin are randomized to receive either add-on AVANDIA or add-on sulfonylurea, and those who have failed sulfonylurea are randomized to receive either add-on AVANDIA or add-on metformin. In RECORD, a total of 2,220 patients are receiving add-on AVANDIA, and 2,227 patients are on one of the add-on regimens not containing AVANDIA.

For these 3 trials, analyses were performed using a composite of major adverse cardiovascular events (myocardial infarction, cardiovascular death, or stroke), referred to hereafter as MACE. This endpoint differed from the meta-analysis' broad endpoint of myocardial ischemic events, more than half of which were angina. Myocardial infarction included adjudicated fatal and nonfatal myocardial infarction plus sudden death. As shown in Figure 2, the results for the 3 endpoints (MACE, MI, and Total Mortality) were not statistically significantly different between AVANDIA and comparators.

Figure 2. Hazard Ratios for the Risk of MACE (Myocardial Infarction, Cardiovascular Death, or Stroke), Myocardial Infarction, and Total Mortality With AVANDIA Compared With a Control Group



RSG = rosiglitazone; SU = sulfonylurea; MET = metformin; RAM = ramipril

In preliminary analyses of the DREAM trial, the incidence of cardiovascular events was higher among subjects who received AVANDIA in combination with ramipril than among subjects who received ramipril alone, as illustrated in Figure 2. This finding was not confirmed in ADOPT and RECORD (active-controlled trials in patients with diabetes) in which 30% and 40% of patients respectively, reported ACE-inhibitor use at baseline.

In their entirety, the available data on the risk of myocardial ischemia are inconclusive. Definitive conclusions regarding this risk await completion of an adequately-designed cardiovascular outcome study.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with AVANDIA or any other oral antidiabetic drug.

5.3 Congestive Heart Failure and Myocardial Ischemia During Coadministration of AVANDIA With Insulin

In studies in which AVANDIA was added to insulin, AVANDIA increased the risk of congestive heart failure and myocardial ischemia. (See Table 2.) Coadministration of AVANDIA

and insulin is not recommended. *[See Indications and Usage (1.2) and Warnings and Precautions (5.1, 5.2).]*

In five, 26-week, controlled, randomized, double-blind trials which were included in the meta-analysis *[see Warnings and Precautions (5.2)]*, patients with type 2 diabetes mellitus were randomized to coadministration of AVANDIA and insulin (N = 867) or insulin (N = 663). In these 5 trials, AVANDIA was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. The total number of patients with emergent congestive heart failure was 21 (2.4%) and 7 (1.1%) in the AVANDIA plus insulin and insulin groups, respectively. The total number of patients with emergent myocardial ischemia was 24 (2.8%) and 9 (1.4%) in the AVANDIA plus insulin and insulin groups, respectively (OR 2.1 [95% CI 0.9, 5.1]). Although the event rate for congestive heart failure and myocardial ischemia was low in the studied population, consistently the event rate was 2-fold or higher with coadministration of AVANDIA and insulin. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of AVANDIA. (See Table 2.)

Table 2. Occurrence of Cardiovascular Events in 5 Controlled Trials of Addition of AVANDIA to Established Insulin Treatment

Event*	**AVANDIA + Insulin (n = 867) n (%)**	**Insulin (n = 663) n (%)**
Congestive heart failure	21 (2.4%)	7 (1.1%)
Myocardial ischemia	24 (2.8%)	9 (1.4%)
Composite of cardiovascular death, myocardial infarction, or stroke	10 (1.2%)	5 (0.8%)
Stroke	5 (0.6%)	4 (0.6%)
Myocardial infarction	4 (0.5%)	1 (0.2%)
Cardiovascular death	4 (0.5%)	1 (0.2%)
All deaths	6 (0.7%)	1 (0.2%)

* Events are not exclusive; i.e., a patient with a cardiovascular death due to a myocardial infarction would be counted in 4 event categories (myocardial ischemia; cardiovascular death, myocardial infarction, or stroke; myocardial infarction; cardiovascular death).

In a sixth, 24-week, controlled, randomized, double-blind trial of AVANDIA and insulin coadministration, insulin was added to AVANDAMET® (rosiglitazone maleate and metformin HCl) (n = 161) and compared to insulin plus placebo (n = 158), after a single-blind 8-week run-in with AVANDAMET. Patients with edema requiring pharmacologic therapy and those with congestive heart failure were excluded at baseline and during the run-in period. In the group receiving AVANDAMET plus insulin, there was one myocardial ischemic event and one sudden

death. No myocardial ischemia was observed in the insulin group, and no congestive heart failure was reported in either treatment group.

5.4 Edema

AVANDIA should be used with caution in patients with edema. In a clinical study in healthy volunteers who received 8 mg of AVANDIA once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo.

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, AVANDIA should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure *[see Boxed Warning, Warnings and Precautions (5.1), and Patient Counseling Information (17.1)]*.

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with AVANDIA, and may be dose related. Patients with ongoing edema were more likely to have adverse events associated with edema if started on combination therapy with insulin and AVANDIA *[see Adverse Reactions (6.1)]*.

5.5 Weight Gain

Dose-related weight gain was seen with AVANDIA alone and in combination with other hypoglycemic agents (Table 3). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure *[see Boxed Warning]*.

Table 3. Weight Changes (kg) From Baseline at Endpoint During Clinical Trials

		Control Group		AVANDIA 4 mg	AVANDIA 8 mg
Monotherapy	**Duration**		**Median (25^{th}, 75^{th} percentile)**	**Median (25^{th}, 75^{th} percentile)**	**Median (25^{th}, 75^{th} percentile)**
	26 weeks	placebo	-0.9 (-2.8, 0.9) N = 210	1.0 (-0.9, 3.6) N = 436	3.1 (1.1, 5.8) N = 439
	52 weeks	sulfonylurea	2.0 (0, 4.0) N = 173	2.0 (-0.6, 4.0) N = 150	2.6 (0, 5.3) N = 157
Combination therapy					
Sulfonylurea	24-26 weeks	sulfonylurea	0 (-1.0, 1.3) N = 1,155	2.2 (0.5, 4.0) N = 613	3.5 (1.4, 5.9) N = 841
Metformin	26 weeks	metformin	-1.4 (-3.2, 0.2) N = 175	0.8 (-1.0, 2.6) N = 100	2.1 (0, 4.3) N = 184
Insulin	26 weeks	insulin	0.9 (-0.5, 2.7) N = 162	4.1 (1.4, 6.3) N = 164	5.4 (3.4, 7.3) N = 150
Sulfonylurea + metformin	26 weeks	sulfonylurea + metformin	0.2 (-1.2, 1.6) N = 272	2.5 (0.8, 4.6) N = 275	4.5 (2.4, 7.3) N = 276

In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed with type 2 diabetes not previously treated with antidiabetic medication *[see Clinical Studies (14.1)]*, the median weight change (25^{th}, 75^{th} percentiles) from baseline at 4 years was 3.5 kg (0.0, 8.1) for AVANDIA, 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin.

In a 24-week study in pediatric patients aged 10 to 17 years treated with AVANDIA 4 to 8 mg daily, a median weight gain of 2.8 kg (25^{th}, 75^{th} percentiles: 0.0, 5.8) was reported.

5.6 Hepatic Effects

Liver enzymes should be measured prior to the initiation of therapy with AVANDIA in all patients and periodically thereafter per the clinical judgment of the healthcare professional. Therapy with AVANDIA should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDIA should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with AVANDIA in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with AVANDIA, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with AVANDIA should be discontinued.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with AVANDIA should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued. *[See Adverse Reactions (6.2, 6.3).]*

5.7 Macular Edema

Macular edema has been reported in postmarketing experience in some diabetic patients who were taking AVANDIA or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings. *[See Adverse Reactions (6.1).]*

5.8 Fractures

In a 4- to 6-year comparative study (ADOPT) of glycemic control with monotherapy in drug-naïve patients recently diagnosed with type 2 diabetes mellitus, an increased incidence of bone fracture was noted in female patients taking AVANDIA. Over the 4- to 6-year period, the incidence of bone fracture in females was 9.3% (60/645) for AVANDIA versus 3.5% (21/605) for glyburide and 5.1% (30/590) for metformin. This increased incidence was noted after the first year of treatment and persisted during the course of the study. The majority of the fractures in the women who received AVANDIA occurred in the upper arm, hand, and foot. These sites of fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip or spine). No increase in fracture rates was observed in men treated with AVANDIA. The risk of fracture should be considered in the care of patients, especially female patients, treated with AVANDIA, and attention given to assessing and maintaining bone health according to current standards of care.

5.9 Hematologic Effects

Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with AVANDIA *[see Adverse Reactions (6.2)]*. The observed changes may be related to the increased plasma volume observed with treatment with AVANDIA.

5.10 Diabetes and Blood Glucose Control

Patients receiving AVANDIA in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response.

5.11 Ovulation

Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some

premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA *[see Use in Specific Populations (8.1)]*. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies; therefore, the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies *[see Nonclinical Toxicology (13.1)]*, the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with AVANDIA should be reviewed.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Adult: In clinical trials, approximately 9,900 patients with type 2 diabetes have been treated with AVANDIA.

Short-Term Trials of AVANDIA as Monotherapy and in Combination With Other Hypoglycemic Agents: The incidence and types of adverse events reported in short-term clinical trials of AVANDIA as monotherapy are shown in Table 4.

Table 4. Adverse Events (≥5% in Any Treatment Group) Reported by Patients in Short-Term* Double-Blind Clinical Trials With AVANDIA as Monotherapy

Preferred Term	AVANDIA Monotherapy	Placebo	Metformin	Sulfonylureas†
	N = 2,526	N = 601	N = 225	N = 626
	%	%	%	%
Upper respiratory tract infection	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
Fatigue	3.6	5.0	4.0	1.9
Sinusitis	3.2	4.5	5.3	3.0
Diarrhea	2.3	3.3	15.6	3.0
Hypoglycemia	0.6	0.2	1.3	5.9

* Short-term trials ranged from 8 weeks to 1 year.

† Includes patients receiving glyburide (N = 514), gliclazide (N = 91), or glipizide (N = 21).

Overall, the types of adverse reactions without regard to causality reported when AVANDIA was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with AVANDIA.

Events of anemia and edema tended to be reported more frequently at higher doses, and

were generally mild to moderate in severity and usually did not require discontinuation of treatment with AVANDIA.

In double-blind studies, anemia was reported in 1.9% of patients receiving AVANDIA as monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas, and 2.2% on metformin. Reports of anemia were greater in patients treated with a combination of AVANDIA and metformin (7.1%) and with a combination of AVANDIA and a sulfonylurea plus metformin (6.7%) compared to monotherapy with AVANDIA or in combination with a sulfonylurea (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies *[see Adverse Reactions (6.2)]*.

In clinical trials, edema was reported in 4.8% of patients receiving AVANDIA as monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. The reporting rate of edema was higher for AVANDIA 8 mg in sulfonylurea combinations (12.4%) compared to other combinations, with the exception of insulin. Edema was reported in 14.7% of patients receiving AVANDIA in the insulin combination trials compared to 5.4% on insulin alone. Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with AVANDIA *[see Boxed Warning and Warnings and Precautions (5.3)]*.

In controlled combination therapy studies with sulfonylureas, mild to moderate hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be severe (<1%). Hypoglycemia was the most frequently reported adverse event in the fixed-dose insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for AVANDIA plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by capillary blood glucose concentration ≤50 mg/dL, were 6% for insulin alone and 12% (4 mg) and 14% (8 mg) for insulin in combination with AVANDIA. *[See Warnings and Precautions (5.10).]*

Long-Term Trial of AVANDIA as Monotherapy: A 4- to 6-year study (ADOPT) compared the use of AVANDIA (n = 1,456), glyburide (n = 1,441), and metformin (n = 1,454) as monotherapy in patients recently diagnosed with type 2 diabetes who were not previously treated with antidiabetic medication. Table 5 presents adverse reactions without regard to causality; rates are expressed per 100 patient-years (PY) exposure to account for the differences in exposure to study medication across the 3 treatment groups.

In ADOPT, fractures were reported in a greater number of women treated with AVANDIA (9.3%, 2.7/100 patient-years) compared to glyburide (3.5%, 1.3/100 patient-years) or metformin (5.1%, 1.5/100 patient-years). The majority of the fractures in the women who received rosiglitazone were reported in the upper arm, hand, and foot. *[See Warnings and Precautions (5.7).]* The observed incidence of fractures for male patients was similar among the 3 treatment groups.

Table 5. On-Therapy Adverse Events (≥5 Events/100 Patient-Years [PY]) in Any Treatment Group Reported in a 4- to 6-Year Clinical Trial of AVANDIA as Monotherapy (ADOPT)

	AVANDIA N = 1,456 PY = 4,954	**Glyburide** N = 1,441 PY = 4,244	**Metformin** N = 1,454 PY = 4,906
Nasopharyngitis	6.3	6.9	6.6
Back pain	5.1	4.9	5.3
Arthralgia	5.0	4.8	4.2
Hypertension	4.4	6.0	6.1
Upper respiratory tract infection	4.3	5.0	4.7
Hypoglycemia	2.9	13.0	3.4
Diarrhea	2.5	3.2	6.8

Pediatric: AVANDIA has been evaluated for safety in a single, active-controlled trial of pediatric patients with type 2 diabetes in which 99 were treated with AVANDIA and 101 were treated with metformin. The most common adverse reactions (>10%) without regard to causality for either AVANDIA or metformin were headache (17% versus 14%), nausea (4% versus 11%), nasopharyngitis (3% versus 12%), and diarrhea (1% versus 13%). In this study, one case of diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in the rosiglitazone group who had FPG of ~300 mg/dL, 2+ ketonuria, and an elevated anion gap.

6.2 Laboratory Abnormalities

Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with AVANDIA (mean decreases in individual studies as much as 1.0 g/dL hemoglobin and as much as 3.3% hematocrit). The changes occurred primarily during the first 3 months following initiation of therapy with AVANDIA or following a dose increase in AVANDIA. The time course and magnitude of decreases were similar in patients treated with a combination of AVANDIA and other hypoglycemic agents or monotherapy with AVANDIA. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. In a single study in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL and 0.95%, respectively) were reported. Small decreases in hemoglobin and hematocrit have also been reported in pediatric patients treated with AVANDIA. White blood cell counts also decreased slightly in adult patients treated with AVANDIA. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with AVANDIA.

Lipids: Changes in serum lipids have been observed following treatment with AVANDIA in adults *[see Clinical Pharmacology (12.2)]*. Small changes in serum lipid parameters were reported in children treated with AVANDIA for 24 weeks.

Serum Transaminase Levels: In pre-approval clinical studies in 4,598 patients treated

with AVANDIA (3,600 patient-years of exposure) and in a long-term 4- to 6-year study in 1,456 patients treated with AVANDIA (4,954 patient-years exposure), there was no evidence of drug-induced hepatotoxicity.

In pre-approval controlled trials, 0.2% of patients treated with AVANDIA had elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with AVANDIA were reversible. Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. *[See Warnings and Precautions (5.6).]*

In the 4- to 6-year ADOPT trial, patients treated with AVANDIA (4,954 patient-years exposure), glyburide (4,244 patient-years exposure), or metformin (4,906 patient-years exposure), as monotherapy, had the same rate of ALT increase to >3X upper limit of normal (0.3 per 100 patient-years exposure).

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the events described below have been identified during post-approval use of AVANDIA. Because these events are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to always establish a causal relationship to drug exposure.

In patients receiving thiazolidinedione therapy, serious adverse events with or without a fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported *[see Boxed Warning and Warnings and Precautions (5.1)]*.

There are postmarketing reports with AVANDIA of hepatitis, hepatic enzyme elevations to 3 or more times the upper limit of normal, and hepatic failure with and without fatal outcome, although causality has not been established.

There are postmarketing reports with AVANDIA of rash, pruritus, urticaria, angioedema, anaphylactic reaction, Stevens-Johnson syndrome, and new onset or worsening diabetic macular edema with decreased visual acuity *[see Warnings and Precautions (5.7)]*.

7 DRUG INTERACTIONS

7.1 CYP2C8 Inhibitors and Inducers

An inhibitor of CYP2C8 (e.g., gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (e.g., rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. *[See Clinical Pharmacology (12.4).]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Careful monitoring of glucose control is essential in such patients. Most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Human Data: Rosiglitazone has been reported to cross the human placenta and be detectable in fetal tissue. The clinical significance of these findings is unknown. There are no adequate and well-controlled studies in pregnant women. AVANDIA should not be used during pregnancy.

Animal Studies: There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or post-natal survival or growth.

8.2 Labor and Delivery

The effect of rosiglitazone on labor and delivery in humans is not known.

8.3 Nursing Mothers

Drug-related material was detected in milk from lactating rats. It is not known whether AVANDIA is excreted in human milk. Because many drugs are excreted in human milk, AVANDIA should not be administered to a nursing woman.

8.4 Pediatric Use

After placebo run-in including diet counseling, children with type 2 diabetes mellitus, aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m^2, were randomized to treatment with 2 mg twice daily of AVANDIA (n = 99) or 500 mg twice daily of metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, FPG decreased in patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of treatment, 49% of patients treated with AVANDIA and 55% of metformin-treated patients had

their dose doubled if FPG >126 mg/dL. For the overall intent-to-treat population, at week 24, the mean change from baseline in HbA1c was -0.14% with AVANDIA and -0.49% with metformin. There was an insufficient number of patients in this study to establish statistically whether these observed mean treatment effects were similar or different. Treatment effects differed for patients naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic therapy (Table 6).

Table 6. Week 24 FPG and HbA1c Change From Baseline Last-Observation-Carried Forward in Children With Baseline HbA1c >6.5%

	Naïve Patients		**Previously-Treated Patients**	
	Metformin	**Rosiglitazone**	**Metformin**	**Rosiglitazone**
	N = 40	N = 45	N = 43	N = 32
FPG (mg/dL)				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted treatment difference* (rosiglitazone–metformin)†		8		21
(95% CI)		(-15, 30)		(-9, 51)
% of patients with ≥30 mg/dL decrease from baseline	43%	27%	44%	28%
HbA1c (%)				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted treatment difference* (rosiglitazone–metformin)†		0.2		0.5
(95% CI)		(-0.6, 0.9)		(-0.2, 1.3)
% of patients with ≥0.7% decrease from baseline	63%	52%	54%	31%

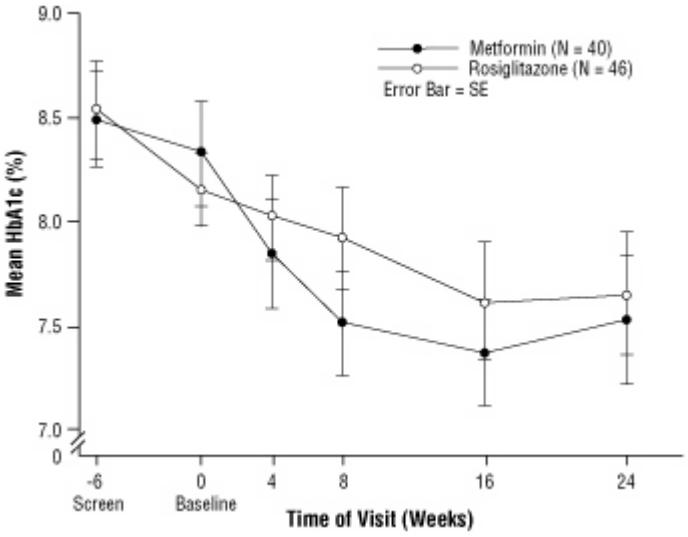
* Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region.

† Positive values for the difference favor metformin.

Treatment differences depended on baseline BMI or weight such that the effects of AVANDIA and metformin appeared more closely comparable among heavier patients. The median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin *[see Warnings and Precautions (5.4)]*. Fifty-four percent of patients treated with rosiglitazone and 32% of patients treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of patients treated with metformin gained ≥5 kg on study.

Adverse events observed in this study are described in *Adverse Reactions (6.1)*.

Figure 3. Mean HbA1c Over Time in a 24-Week Study of AVANDIA and Metformin in Pediatric Patients — Drug-Naïve Subgroup



8.5 Geriatric Use

Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone *[see Clinical Pharmacology (12.3)]*. Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older (≥65 years) and younger (<65 years) patients were observed.

10 OVERDOSAGE

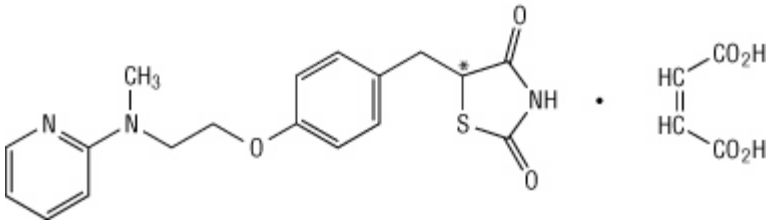
Limited data are available with regard to overdosage in humans. In clinical studies in volunteers, AVANDIA has been administered at single oral doses of up to 20 mg and was well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

11 DESCRIPTION

AVANDIA (rosiglitazone maleate) is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. AVANDIA improves glycemic control while reducing circulating insulin levels.

Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors.

Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The structural formula of rosiglitazone maleate is:



The molecular formula is $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Each pentagonal film-coated TILTAB tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are: Hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Synthetic red and yellow iron oxides and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

In animal models, the antidiabetic activity of rosiglitazone was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. Pharmacological studies in animal models indicate that rosiglitazone inhibits hepatic gluconeogenesis. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

12.2 Pharmacodynamics

Patients with lipid abnormalities were not excluded from clinical trials of AVANDIA. In all 26-week controlled trials, across the recommended dose range, AVANDIA as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls

(Table 7).

Increases in LDL occurred primarily during the first 1 to 2 months of therapy with AVANDIA and LDL levels remained elevated above baseline throughout the trials. In contrast, HDL continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of therapy and then appeared to decrease over time. Because of the temporal nature of lipid changes, the 52-week glyburide-controlled study is most pertinent to assess long-term effects on lipids. At baseline, week 26, and week 52, mean LDL/HDL ratios were 3.1, 3.2, and 3.0, respectively, for AVANDIA 4 mg twice daily. The corresponding values for glyburide were 3.2, 3.1, and 2.9. The differences in change from baseline between AVANDIA and glyburide at week 52 were statistically significant.

The pattern of LDL and HDL changes following therapy with AVANDIA in combination with other hypoglycemic agents were generally similar to those seen with AVANDIA in monotherapy.

The changes in triglycerides during therapy with AVANDIA were variable and were generally not statistically different from placebo or glyburide controls.

Table 7. Summary of Mean Lipid Changes in 26-Week Placebo-Controlled and 52-Week Glyburide-Controlled Monotherapy Studies

	Placebo-Controlled Studies Week 26			**Glyburide-Controlled Study Week 26 and Week 52**			
	Placebo	**AVANDIA**		**Glyburide Titration**		**AVANDIA 8 mg**	
		4 mg daily*	8 mg daily*	Wk 26	Wk 52	Wk 26	Wk 52
Free fatty acids							
N	207	428	436	181	168	166	145
Baseline (mean)	18.1	17.5	17.9	26.4	26.4	26.9	26.6
% Change from baseline (mean)	+0.2%	-7.8%	-14.7%	-2.4%	-4.7%	-20.8%	-21.5%
LDL							
N	190	400	374	175	160	161	133
Baseline (mean)	123.7	126.8	125.3	142.7	141.9	142.1	142.1
% Change from baseline (mean)	+4.8%	+14.1%	+18.6%	-0.9%	-0.5%	+11.9%	+12.1%
HDL							
N	208	429	436	184	170	170	145
Baseline (mean)	44.1	44.4	43.0	47.2	47.7	48.4	48.3
% Change from baseline (mean)	+8.0%	+11.4%	+14.2%	+4.3%	+8.7%	+14.0%	+18.5%

* Once daily and twice daily dosing groups were combined.

12.3 Pharmacokinetics

Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (Table 8). The elimination half-life is 3 to 4 hours and is independent of dose.

Table 8. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (N = 32)

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
$AUC_{0\text{-}inf}$ [ng•hr/mL]	358 (112)	733 (184)	2,971 (730)	2,890 (795)
C_{max} [ng/mL]	76 (13)	156 (42)	598 (117)	432 (92)
Half-life [hr]	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F* [L/hr]	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)

* CL/F = Oral clearance.

Absorption: The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease in C_{max} and a delay in T_{max} (1.75 hours). These changes are not likely to be clinically significant; therefore, AVANDIA may be administered with or without food.

Distribution: The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Metabolism: Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone.

In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

Excretion: Following oral or intravenous administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 103 to 158 hours.

Population Pharmacokinetics in Patients With Type 2 Diabetes: Population pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not

influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and Vss/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

Special Populations: *Geriatric:* Results of the population pharmacokinetic analysis (n = 716 <65 years; n = 331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

Gender: Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (n = 405) was approximately 6% lower compared to male patients of the same body weight (n = 642).

As monotherapy and in combination with metformin, AVANDIA improved glycemic control in both males and females. In metformin combination studies, efficacy was demonstrated with no gender differences in glycemic response.

In monotherapy studies, a greater therapeutic response was observed in females; however, in more obese patients, gender differences were less evident. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target PPARγ is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to AVANDIA in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

Hepatic Impairment: Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and $AUC_{0\text{-}inf}$ were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline *[see Warnings and Precautions (5.6)]*.

Pediatric: Pharmacokinetic parameters of rosiglitazone in pediatric patients were established using a population pharmacokinetic analysis with sparse data from 96 pediatric patients in a single pediatric clinical trial including 33 males and 63 females with ages ranging from 10 to 17 years (weights ranging from 35 to 178.3 kg). Population mean CL/F and V/F of rosiglitazone were 3.15 L/hr and 13.5 L, respectively. These estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis.

Renal Impairment: There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients receiving AVANDIA. Since metformin is contraindicated in patients with renal impairment, coadministration of metformin with AVANDIA is contraindicated in

these patients.

Race: Results of a population pharmacokinetic analysis including subjects of Caucasian, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

12.4 Drug-Drug Interactions

Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P450: In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. AVANDIA (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Gemfibrozil: Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be needed when gemfibrozil is introduced *[see Drug Interactions (7.1)]*.

Rifampin: Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of rosiglitazone (8 mg) alone *[see Drug Interactions (7.1)]*.[4]

Glyburide: AVANDIA (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of AVANDIA (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased following coadministration of AVANDIA.

Glimepiride: Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of AVANDIA. No clinically significant reductions in glimepiride AUC and C_{max} were observed after repeat doses of AVANDIA (8 mg once daily) for 8 days in healthy adult subjects.

Metformin: Concurrent administration of AVANDIA (2 mg twice daily) and metformin (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state pharmacokinetics of either metformin or rosiglitazone.

Acarbose: Coadministration of acarbose (100 mg three times daily) for 7 days in healthy volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of AVANDIA.

Digoxin: Repeat oral dosing of AVANDIA (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

Warfarin: Repeat dosing with AVANDIA had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with AVANDIA.

Ranitidine: Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the pharmacokinetics of either single oral or intravenous doses of rosiglitazone in healthy volunteers. These results suggest that the absorption of oral rosiglitazone is not altered in conditions accompanied by increases in gastrointestinal pH.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: A 2-year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended human daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge,

lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

13.2 Animal Toxicology

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

14 CLINICAL STUDIES

14.1 Monotherapy

In clinical studies, treatment with AVANDIA resulted in an improvement in glycemic control, as measured by FPG and HbA1c, with a concurrent reduction in insulin and C-peptide. Postprandial glucose and insulin were also reduced. This is consistent with the mechanism of action of AVANDIA as an insulin sensitizer.

The maximum recommended daily dose is 8 mg. Dose-ranging studies suggested that no additional benefit was obtained with a total daily dose of 12 mg.

Short-Term Clinical Studies: A total of 2,315 patients with type 2 diabetes, previously treated with diet alone or antidiabetic medication(s), were treated with AVANDIA as monotherapy in 6 double-blind studies, which included two 26-week placebo-controlled studies, one 52-week glyburide-controlled study, and 3 placebo-controlled dose-ranging studies of 8 to 12 weeks duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week placebo run-in period prior to randomization.

Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes (n = 1,401) with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL [101 to 425 mg/dL] and mean baseline HbA1c 8.9% [5.2% to 16.2%]), were conducted. Treatment with AVANDIA produced statistically significant improvements in FPG and HbA1c compared to baseline and relative to placebo. Data from one of these studies are summarized in Table 9.

Table 9. Glycemic Parameters in a 26-Week Placebo-Controlled Trial

		AVANDIA		AVANDIA	
	Placebo	**4 mg once daily**	**2 mg twice daily**	**8 mg once daily**	**4 mg twice daily**
	N = 173	N = 180	N = 186	N = 181	N = 187
FPG (mg/dL)					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference from placebo (adjusted mean)	–	-31*	-43*	-49*	-62*
% of patients with ≥30 mg/dL decrease from baseline	19%	45%	54%	58%	70%
HbA1c (%)					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	-0.1	-0.3	-0.7
Difference from placebo (adjusted mean)	–	-0.8*	-0.9*	-1.1*	-1.5*
% of patients with ≥0.7% decrease from baseline	9%	28%	29%	39%	54%

* $p<0.0001$ compared to placebo.

When administered at the same total daily dose, AVANDIA was generally more effective in reducing FPG and HbA1c when administered in divided doses twice daily compared to once daily doses. However, for HbA1c, the difference between the 4 mg once daily and 2 mg twice daily doses was not statistically significant.

Long-Term Clinical Studies: Long-term maintenance of effect was evaluated in a 52-week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were randomized to treatment with AVANDIA 2 mg twice daily (N = 195) or AVANDIA 4 mg twice daily (N = 189) or glyburide (N = 202) for 52 weeks. Patients receiving glyburide were given an initial dosage of either 2.5 mg/day or 5.0 mg/day. The dosage was then titrated in 2.5 mg/day increments over the next 12 weeks, to a maximum dosage of 15.0 mg/day in order to optimize glycemic control. Thereafter, the glyburide dose was kept constant.

The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a statistically significant improvement in glycemic control from baseline (Figure 4 and Figure 5). At the end of week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/dL and -0.53% with AVANDIA 4 mg twice daily; -25.4 mg/dL and -0.27% with AVANDIA 2 mg twice daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between AVANDIA 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with AVANDIA; however, this effect was less durable over time. The improvement in glycemic control seen with AVANDIA 4 mg twice daily

at week 26 was maintained through week 52 of the study.

Figure 4. Mean FPG Over Time in a 52-Week Glyburide-Controlled Study

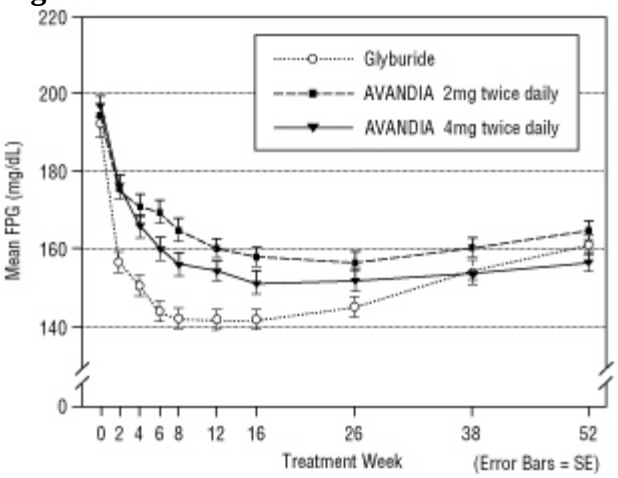
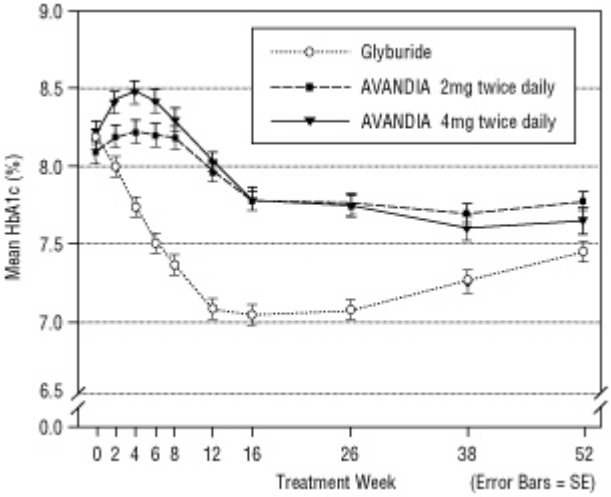


Figure 5. Mean HbA1c Over Time in a 52-Week Glyburide-Controlled Study



Hypoglycemia was reported in 12.1% of glyburide-treated patients versus 0.5% (2 mg twice daily) and 1.6% (4 mg twice daily) of patients treated with AVANDIA. The improvements in glycemic control were associated with a mean weight gain of 1.75 kg and 2.95 kg for patients treated with 2 mg and 4 mg twice daily of AVANDIA, respectively, versus 1.9 kg in glyburide-treated patients. In patients treated with AVANDIA, C-peptide, insulin, pro-insulin, and pro-insulin split products were significantly reduced in a dose-ordered fashion, compared to an increase in the glyburide-treated patients.

A Diabetes Outcome Progression Trial (ADOPT) was a multicenter, double-blind, controlled trial (N = 4,351) conducted over 4 to 6 years to compare the safety and efficacy of AVANDIA, metformin, and glyburide monotherapy in patients recently diagnosed with type 2 diabetes mellitus (≤3 years) inadequately controlled with diet and exercise. The mean age of

patients in this trial was 57 years and the majority of patients (83%) had no known history of cardiovascular disease. The mean baseline FPG and HbA1c were 152 mg/dL and 7.4%, respectively. Patients were randomized to receive either AVANDIA 4 mg once daily, glyburide 2.5 mg once daily, or metformin 500 mg once daily, and doses were titrated to optimal glycemic control up to a maximum of 4 mg twice daily for AVANDIA, 7.5 mg twice daily for glyburide, and 1,000 mg twice daily for metformin. The primary efficacy outcome was time to consecutive FPG >180 mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study medication or time to inadequate glycemic control, as determined by an independent adjudication committee.

The cumulative incidence of the primary efficacy outcome at 5 years was 15% with AVANDIA, 21% with metformin, and 34% with glyburide (hazard ratio 0.68 [95% CI 0.55, 0.85] versus metformin, HR 0.37 [95% CI 0.30, 0.45] versus glyburide).

Cardiovascular and adverse event data (including effects on body weight and bone fracture) from ADOPT for AVANDIA, metformin, and glyburide are described in *Warnings and Precautions (5.2, 5.5, and 5.8)* and *Adverse Reactions (6.1)*, respectively. As with all medications, efficacy results must be considered together with safety information to assess the potential benefit and risk for an individual patient.

14.2 Combination With Metformin or Sulfonylurea

The addition of AVANDIA to either metformin or sulfonylurea resulted in significant reductions in hyperglycemia compared to either of these agents alone. These results are consistent with an additive effect on glycemic control when AVANDIA is used as combination therapy.

Combination With Metformin: A total of 670 patients with type 2 diabetes participated in two 26-week, randomized, double-blind, placebo/active-controlled studies designed to assess the efficacy of AVANDIA in combination with metformin. AVANDIA, administered in either once daily or twice daily dosing regimens, was added to the therapy of patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin.

In one study, patients inadequately controlled on 2.5 grams/day of metformin (mean baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive 4 mg of AVANDIA once daily, 8 mg of AVANDIA once daily, or placebo in addition to metformin. A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of metformin and 4 mg of AVANDIA once daily and 8 mg of AVANDIA once daily, versus patients continued on metformin alone (Table 10).

Table 10. Glycemic Parameters in a 26-Week Combination Study of AVANDIA Plus Metformin

	Metformin	AVANDIA 4 mg once daily + metformin	AVANDIA 8 mg once daily + metformin
	N = 113	N = 116	N = 110
FPG (mg/dL)			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	-33	-48
Difference from metformin alone (adjusted mean)	–	-40*	-53*
% of patients with ≥30 mg/dL decrease from baseline	20%	45%	61%
HbA1c (%)			
Baseline (mean)	8.6	8.9	8.9
Change from baseline (mean)	0.5	-0.6	-0.8
Difference from metformin alone (adjusted mean)	–	-1.0*	-1.2*
% of patients with ≥0.7% decrease from baseline	11%	45%	52%

* $p<0.0001$ compared to metformin.

In a second 26-week study, patients with type 2 diabetes inadequately controlled on 2.5 grams/day of metformin who were randomized to receive the combination of AVANDIA 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect for HbA1c of -0.8% over metformin alone. The combination of metformin and AVANDIA resulted in lower levels of FPG and HbA1c than either agent alone.

Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin and who were switched to monotherapy with AVANDIA demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c. In this group, increases in LDL and VLDL were also seen.

Combination With a Sulfonylurea: A total of 3,457 patients with type 2 diabetes participated in ten 24- to 26-week randomized, double-blind, placebo/active-controlled studies and one 2-year double-blind, active-controlled study in elderly patients designed to assess the efficacy and safety of AVANDIA in combination with a sulfonylurea. AVANDIA 2 mg, 4 mg, or 8 mg daily was administered, either once daily (3 studies) or in divided doses twice daily (7 studies), to patients inadequately controlled on a submaximal or maximal dose of sulfonylurea.

In these studies, the combination of AVANDIA 4 mg or 8 mg daily (administered as

single or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 11 shows pooled data for 8 studies in which AVANDIA added to sulfonylurea was compared to placebo plus sulfonylurea.

Table 11. Glycemic Parameters in 24- to 26-Week Combination Studies of AVANDIA Plus Sulfonylurea

Twice Daily Divided Dosing (5 Studies)	**Sulfonylurea**	**AVANDIA 2 mg twice daily + sulfonylurea**	**Sulfonylurea**	**AVANDIA 4 mg twice daily + sulfonylurea**
	N = 397	N = 497	N = 248	N = 346
FPG (mg/dL)				
Baseline (mean)	204	198	188	187
Change from baseline (mean)	11	-29	8	-43
Difference from sulfonylurea alone (adjusted mean)	–	-42*	–	-53*
% of patients with ≥30 mg/dL decrease from baseline	17%	49%	15%	61%
HbA1c (%)				
Baseline (mean)	9.4	9.5	9.3	9.6
Change from baseline (mean)	0.2	-1.0	0.0	-1.6
Difference from sulfonylurea alone (adjusted mean)	–	-1.1*	–	-1.4*
% of patients with ≥0.7% decrease from baseline	21%	60%	23%	75%
Once Daily Dosing (3 Studies)	**Sulfonylurea**	**AVANDIA 4 mg once daily + sulfonylurea**	**Sulfonylurea**	**AVANDIA 8 mg once daily + sulfonylurea**
	N = 172	N = 172	N = 173	N = 176
FPG (mg/dL)				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	–	-47*	–	-66*
% of patients with ≥30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline (mean)	0.4	-0.5	0.1	-1.2
Difference from sulfonylurea alone (adjusted mean)	–	-0.9*	–	-1.4*
% of patients with ≥0.7% decrease from baseline	11%	36%	20%	68%

* $p<0.0001$ compared to sulfonylurea alone.

One of the 24- to 26-week studies included patients who were inadequately controlled on maximal doses of glyburide and switched to 4 mg of AVANDIA daily as monotherapy; in this group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.

In a 2-year double-blind study, elderly patients (aged 59 to 89 years) on half-maximal sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of AVANDIA (n = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (n = 110), to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and 7.72%, respectively, for the AVANDIA plus glipizide arm and 159 mg/dL and 7.65%, respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG ≥180 mg/dL) occurred in a significantly lower proportion of patients (2%) on AVANDIA plus glipizide compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on combination therapy completed the 2 years of therapy while only 51% completed on glipizide monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year study period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for HbA1c compared to no change on the glipizide arm.

14.3 Combination With Sulfonylurea Plus Metformin

In two 24- to 26-week, double-blind, placebo-controlled, studies designed to assess the efficacy and safety of AVANDIA in combination with sulfonylurea plus metformin, AVANDIA 4 mg or 8 mg daily, was administered in divided doses twice daily, to patients inadequately controlled on submaximal (10 mg) and maximal (20 mg) doses of glyburide and maximal dose of metformin (2 g/day). A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of sulfonylurea plus metformin and 4 mg of AVANDIA and 8 mg of AVANDIA versus patients continued on sulfonylurea plus metformin, as shown in Table 12.

Table 12. Glycemic Parameters in a 26-Week Combination Study of AVANDIA Plus Sulfonylurea and Metformin

	Sulfonylurea + metformin	**AVANDIA 2 mg twice daily + sulfonylurea + metformin**	**AVANDIA 4 mg twice daily + sulfonylurea + metformin**
	N = 273	N = 276	N = 277
FPG (mg/dL)			
Baseline (mean)	189	190	192
Change from baseline (mean)	14	-19	-40
Difference from sulfonylurea plus metformin (adjusted mean)	–	-30*	-52*
% of patients with ≥30 mg/dL decrease from baseline	16%	46%	62%
HbA1c (%)			
Baseline (mean)	8.7	8.6	8.7
Change from baseline (mean)	0.2	-0.4	-0.9
Difference from sulfonylurea plus metformin (adjusted mean)	–	-0.6*	-1.1*
% of patients with ≥0.7% decrease from baseline	16%	39%	63%

* $p<0.0001$ compared to placebo.

15 REFERENCES

1. Food and Drug Administration Briefing Document. Joint meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees. July 30, 2007.
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3. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. *NEJM* 2007;357:1-11.
4. Park JY, Kim KA, Kang MH, et al. Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004;75:157-162.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each pentagonal film-coated TILTAB tablet contains rosiglitazone as the maleate as

follows: 2 mg–pink, debossed with SB on one side and 2 on the other; 4 mg–orange, debossed with SB on one side and 4 on the other; 8 mg–red-brown, debossed with SB on one side and 8 on the other.
2 mg bottles of 60: NDC 0029-3158-18
4 mg bottles of 30: NDC 0029-3159-13
4 mg bottles of 90: NDC 0029-3159-00
8 mg bottles of 30: NDC 0029-3160-13
8 mg bottles of 90: NDC 0029-3160-59

Store at 25°C (77°F); excursions 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

17.1 Patient Advice

Patients should be informed of the following:

- AVANDIA is not recommended for patients with symptoms of heart failure.
- Patients with more severe heart failure (NYHA Class 3 or 4) cannot start AVANDIA as the risks exceed any potential benefits in such patients.
- Results of a set of clinical studies suggest that treatment with AVANDIA is associated with an increased risk for myocardial ischemic events, such as angina or myocardial infarction (heart attack), especially in patients taking insulin or nitrates. Because this risk has not been confirmed or excluded in different long-term trials, definitive conclusions regarding this risk await completion of an adequately-designed cardiovascular outcome study.
- AVANDIA is not recommended for patients who are taking nitrates or insulin.
- There are multiple medications available to treat type 2 diabetes. The benefits and risks of each available diabetes medication should be taken into account when choosing a particular diabetes medication for a given patient.
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with AVANDIA or any other oral antidiabetic drug.
- Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but in maintaining the efficacy of drug therapy.
- It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. It can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of AVANDIA.
- Blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgment of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician.
- Patients who experience an unusually rapid increase in weight or edema or who develop

shortness of breath or other symptoms of heart failure while on AVANDIA should immediately report these symptoms to their physician.
- AVANDIA can be taken with or without meals.
- When using AVANDIA in combination with other hypoglycemic agents, the risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.
- Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

17.2 FDA-Approved Medication Guide

See separate leaflet.

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GlaxoSmithKline
Research Triangle Park, NC 27709

MEDICATION GUIDE
AVANDIA® (ah-VAN-dee-a)
rosiglitazone maleate tablets

Read this Medication Guide carefully before you start taking AVANDIA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about AVANDIA, ask your doctor or pharmacist.

What is the most important information I should know about AVANDIA?
AVANDIA is a prescription medicine to treat adults with diabetes. It helps to control high blood sugar. (See "What is AVANDIA?"). It is important that you take AVANDIA exactly how it is prescribed by your doctor to best treat your diabetes.

AVANDIA may cause serious side effects, including:

New or worse heart failure
- AVANDIA can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start AVANDIA.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, AVANDIA may not be right for you.

Call your doctor right away if you have any of the following:
- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- unusual tiredness

Other heart problems
AVANDIA may raise the risk of heart problems related to reduced blood flow to the heart. These include possible increases in the risk of heart-related chest pain (angina) or "heart attack" (myocardial infarction). This risk seemed to be higher in people who took AVANDIA with insulin or with nitrate medicines. Most people who take insulin or nitrate medicines should not also take AVANDIA.
- If you have chest pain or a feeling of chest pressure, get medical help right away, no matter what diabetes medicines you are taking.
- People with diabetes have a greater risk for heart problems. It is important to work with your doctor to manage other conditions, such as high blood pressure or high cholesterol.

AVANDIA can have other serious side effects. Be sure to read the section below "What are possible side effects of AVANDIA?".

What is AVANDIA?
AVANDIA is a prescription medicine used with diet and exercise to treat adults with type 2 ("adult-onset" or "non-insulin dependent") diabetes mellitus ("high blood sugar"). AVANDIA helps to control high blood sugar. AVANDIA may be used alone or with other diabetes medicines. AVANDIA can help your body respond better to insulin made in your body. AVANDIA does not cause your body to make more insulin.

- For AVANDIA to work best, it is very important to exercise, lose extra weight, and follow the diet recommended by your doctor.
- AVANDIA has not been studied enough in children under 18 years of age to know if it is safe or effective in children.
- AVANDIA is not for people with type 1 diabetes mellitus or to treat a condition called diabetic ketoacidosis.

Who should not take AVANDIA?
Many people with heart failure should not start taking AVANDIA. See "What should I tell my doctor before taking AVANDIA?".

What should I tell my doctor before taking AVANDIA?
Before starting AVANDIA, ask your doctor about what the choices are for diabetes medicines, and what the expected benefits and possible risks are for you in particular.

Before taking AVANDIA, tell your doctor about all your medical conditions, including if you:

- **have heart problems or heart failure.**
- **have type 1 ("juvenile") diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin.
- **have a type of diabetic eye disease called macular edema** (swelling of the back of the eye).
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking AVANDIA and during treatment as needed.
- **had liver problems while taking REZULIN® (troglitazone), another medicine for diabetes.**
- **are pregnant or plan to become pregnant.** AVANDIA should not be used during pregnancy. It is not known if AVANDIA can harm your unborn baby. You and your doctor should talk about the best way to control your diabetes during pregnancy. If you are a premenopausal woman (before the "change of life") who does not have regular monthly periods, AVANDIA may increase your chances of becoming pregnant. Talk to your doctor about birth control choices while taking AVANDIA. Tell your doctor right away if you

become pregnant while taking AVANDIA.
- **are breast-feeding or planning to breast-feed.** It is not known if AVANDIA passes into breast milk. You should not use AVANDIA while breast-feeding.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements. AVANDIA and certain other medicines can affect each other and may lead to serious side effects including high or low blood sugar, or heart problems. Especially tell your doctor if you take:
- **insulin.**
- **nitrate medicines** such as nitroglycerin or isosorbide to treat a type of chest pain called angina.
- **any medicines for high blood pressure, high cholesterol or heart failure, or for prevention of heart disease or stroke.**

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist before you start a new medicine. They will tell you if it is alright to take AVANDIA with other medicines.

How should I take AVANDIA?
- Take AVANDIA exactly as prescribed. Your doctor will tell you how many tablets to take and how often. The usual daily starting dose is 4 mg a day taken one time each day or 2 mg taken two times each day. Your doctor may need to adjust your dose until your blood sugar is better controlled.
- AVANDIA may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled.
- Take AVANDIA with or without food.
- It can take 2 weeks for AVANDIA to start lowering blood sugar. It may take 2 to 3 months to see the full effect on your blood sugar level.
- If you miss a dose of AVANDIA, take it as soon as you remember, unless it is time to take your next dose. Take your next dose at the usual time. Do not take double doses to make up for a missed dose.
- If you take too much AVANDIA, call your doctor or poison control center right away.
- Test your blood sugar regularly as your doctor tells you.
- Diet and exercise can help your body use its blood sugar better. It is important to stay on your recommended diet, lose extra weight, and get regular exercise while taking AVANDIA.
- Your doctor should do blood tests to check your liver before you start AVANDIA and during treatment as needed. Your doctor should also do regular blood sugar tests (for example, “A1C”) to monitor your response to AVANDIA.

What are possible side effects of AVANDIA?

AVANDIA may cause serious side effects including:

- **New or worse heart failure.** See “What is the most important information I should know about AVANDIA?”.
- **Other heart problems.** AVANDIA may increase the risk of heart problems related to reduced blood flow to the heart. These include possible increases in the risk of heart-related chest pain (angina) or "heart attack" (myocardial infarction). See “What is the most important information I should know about AVANDIA?”.
- **Swelling (edema).** AVANDIA can cause swelling due to fluid retention. See “What is the most important information I should know about AVANDIA?”.
- **Weight gain.** AVANDIA can cause weight gain that may be due to fluid retention or extra body fat. Weight gain can be a serious problem for people with certain conditions including heart problems. See “What is the most important information I should know about AVANDIA?”.
- **Liver problems.** It is important for your liver to be working normally when you take AVANDIA. Your doctor should do blood tests to check your liver before you start taking AVANDIA and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes.
- **Macular edema** (a diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly. Very rarely, some people have experienced vision changes due to swelling in the back of the eye while taking AVANDIA.
- **Fractures (broken bones),** usually in the hand, upper arm or foot, in females. Talk to your doctor for advice on how to keep your bones healthy.
- **Low red blood cell count (anemia).**
- **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness or hunger may mean that your blood sugar is too low. This can happen if you skip meals, if you use another medicine that lowers blood sugar, or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Ovulation** (release of egg from an ovary in a woman) leading to pregnancy. Ovulation may happen in premenopausal women who do not have regular monthly periods. This can increase the chance of pregnancy. See “What should I tell my doctor before taking AVANDIA?”.

The most common side effects of AVANDIA reported in clinical trials included cold-like symptoms and headache.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AVANDIA?

- Store AVANDIA at room temperature, 59° to 86°F (15° to 30°C). Keep AVANDIA in the container it comes in.
- Safely, throw away AVANDIA that is out of date or no longer needed.
- Keep AVANDIA and all medicines out of the reach of children.

General information about AVANDIA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AVANDIA for a condition for which it was not prescribed. Do not give AVANDIA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes important information about AVANDIA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about AVANDIA that is written for healthcare professionals. You can also find out more about AVANDIA by calling 1-888-825-5249 or visiting the website www.avandia.com.

What are the ingredients in AVANDIA?

Active Ingredient: Rosiglitazone maleate.
Inactive Ingredients: Hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Synthetic red and yellow iron oxides and talc.

Always check to make sure that the medicine you are taking is the correct one. AVANDIA tablets are triangles with rounded corners and look like this:

2 mg strength tablets – pink with “SB” on one side and “2” on the other.
4 mg strength tablets – orange with “SB” on one side and “4” on the other.
8 mg strength tablets – red-brown with “SB” on one side and “8” on the other.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

GlaxoSmithKline
Research Triangle Park, NC 27709

October 2008
AVD:4MG

9.3. Appendix 3. Details of Observational Studies (Tables and Figures)

Table 15 Studies Comparing the Risk of MI in Rosiglitazone Compared to Other Anti-glycemic Agents

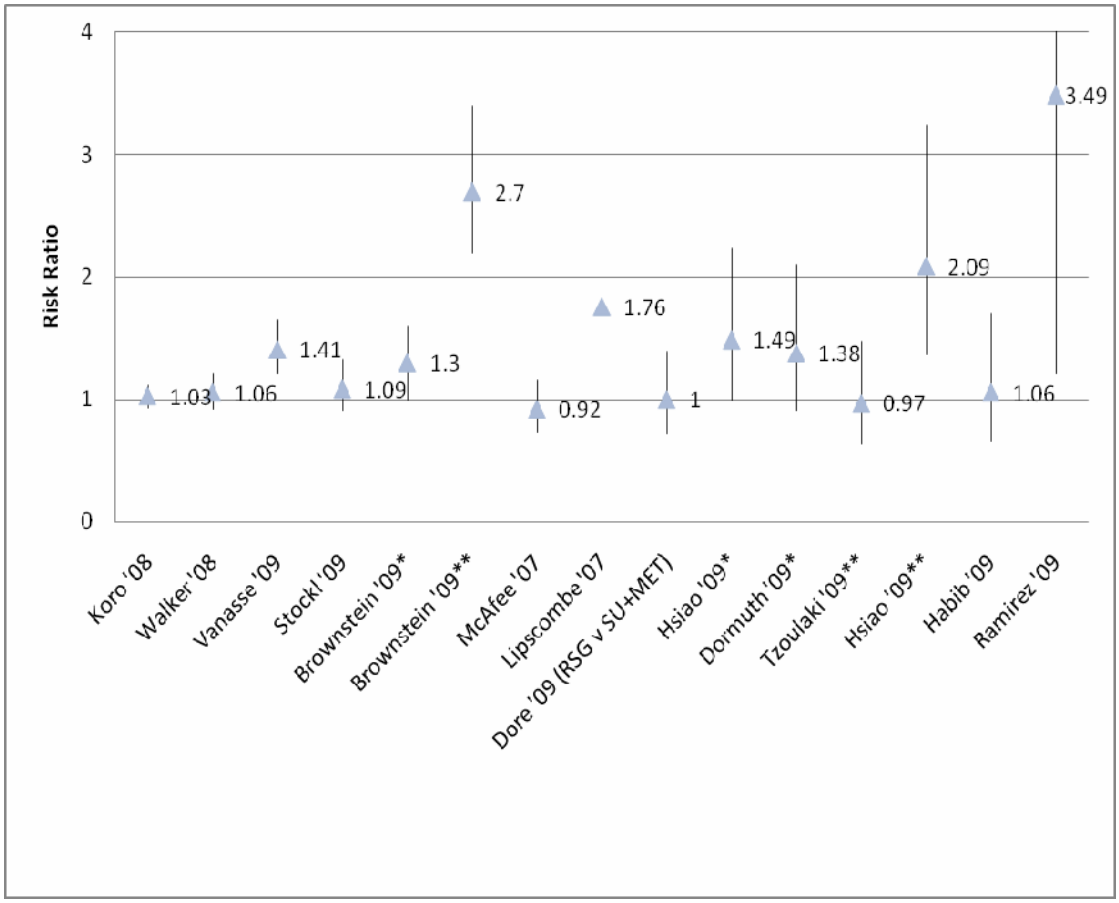
Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI) for MI	Major Study Limitations
Lipscombe 2007	Nested case-control	Health databases from Ontario, Canada (Ontario Drug Benefit database, National Ambulatory Care Reporting System database, Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan database, Registered Persons Database, Ontario Diabetes Database) 2002-2006	TZD mono 229 TZD combination 1 463 Other OHA mono 57 177 Other OHA combination 30 076	Current RSG mono vs. Current other OHA combination 1.76 (1.27-2.44)	- Disproportionately small number of TZD subjects; The number of subjects for the primary exposure of interest, TZD monotherapy, was 229 compared to other oral hypoglycemic agents monotherapy (N= 57,177). -Lack of internal validity because current users of monotherapy (who should be at the early stages of their diabetes) were at increased risk for acute myocardial infarction, whereas the TZD combination therapy (typically more advanced) were at lower risk.
McAfee 2007	Propensity Matched Retrospective Cohort	Ingenix Research Database 2000-2005	RSG 12 874 Non-TZD 20 489	RSG vs. Non-TZD 0.92 (0.73-1.16)	-Statistical power limited by the rarity of the outcomes especially in the insulin combination cohorts
Koro 2008	Nested case-control	Integrated Healthcare Information Services (IHCIS) 1999-2006	Diabetes cohort 891 901 MI cases 9 870 MI controls 29 610	RSG vs. Antidiabetic therapy 3-month exposure 1.03 (0.93-1.12)* <6-month exposure 0.88 (0.77-1.01) 6-12 month exposure 0.92 (0.80-1.05) >12-month exposure 1.15 (1.04-1.27) * primary analysis	-Potential for residual bias due to unmeasured predictors of MI (e.g., BMI, smoking status, duration of diabetes)

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI) for MI	Major Study Limitations
Walker 2008	Balanced Retrospective Cohort	Pharmetrics 2000-2007	RSG 57 381 PIO 51 641 Non-TZD 293 823	RSG vs. Non-RSG 1.06 (0.92-1.21)	-Duration on a given anti-glycemic regimen short (average on treatment time <1 yr for all regimens)
Brownstein 2010	Retrospective Cohort	Partners Healthcare System including Brigham and Women's and Massachusetts General Hospital Research Patient Data Registry 2000-2006	RSG 1 879 MET 12 490 SU 11 200 PIO 806	RSG vs. SU 1.3 (1.0-1.6) RSG vs. MET 2.7 (2.2-3.4)	-Lack of complete prescription data for all individual patients -Low specificity for detection of myocardial infarction events (74%) -Low sample size for RSG exposed subjects
Dore 2009	Nested case-control	Medicaid Analytic Extract (MAX) database 2001-2002	Case 2 316 Control 9 700	RSG within 180 days before index date vs. MET+SU prevalent use 1.00(0.72-1.39)	-Baseline CV risks very different for cases and controls -Wide 95% CIs -Subjects differ from the general population
Dormuth 2009	Nested case-control in prior MET users	British Columbia databases (PharmaNet, BC Ministry of Health Database, Canadian Institute of Health Information) 2003-2007	Case 2 244 Control 8 903	RSG vs. SU (1-6 months) 1.38 (0.91-2.10)	-Small sample size for PIO group (use of PIO was half that of RSG)
Habib 2009	Time-updated propensity score adjusted cohort	Henry Ford A large vertically integrated health system 2000-2007	Entire Cohort 19 171 RSG 1 056 PIO 3 217	RSG vs. No RSG 1.06 (0.66-1.70)	-RSG and PIO groups might be different in important ways including a greater percentage of the RSG group having a history of various cardiovascular diseases compared to the PIO group -Short follow-up (293 days for RSG, 294 days for PIO). -Wide 95% CIs for RSG and TZDs -Results regarding PIO and CHF not consistent with labeled class effect of TZD -PIO group 3 times greater in size -Actual duration of exposure not known

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI) for MI	Major Study Limitations
Hsiao 2009	Population based Retrospective Cohort	Taiwan's National Health Insurance Claims database 2000-2005	RSG mono 2 093 PIO mono 495 SU-based therapy 104 023 MET-based therapy 49 626 SU+MET-based therapy 317 246	RSG vs. SU 1.49 (0.99-2.24) RSG vs. MET 2.09 (1.36-3.24)	-Small sample of RSG exposed patients; only 0.44% of the study sample was on RSG monotherapy. -A much greater proportion of the subjects in the RSG group had previous history of cardiovascular events (e.g. 6.59% of any CV events 1 year prior in RSG vs. 1.51-3.55% in non-TZD)
Ramirez 2009	Retrospective Cohort	Dialysis Outcomes and Practice Patterns Study I and II in US 1999-2004	RSG 177 PIO 118 Non-TZD OHA 2 050	RSG vs. Non-TZD OHAs 3.49 (1.21-10.04)	- Small number of RSG exposed subject (N=177) representing only 7% of the study population - Missing data on the type of oral hypoglycemic agents for 47% of patients included in the study. -Significantly higher mean plasma glucose level for RSG patients at baseline compared to non-TZD oral hypoglycemic agents; -RSG patients may have diabetes that is more difficult to control and carries a higher risk of cardiovascular outcomes.
Stockl 2009	Nested case-control	Prescription Solutions 2002-2006	Case 1 681 Control 6 653	RSG vs. No TZD 1.09 (0.90-1.32)	-AMI risk increased with recent RSG exposure but not with current exposure -Patients who died of AMI before reaching the hospital not captured

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI) for MI	Major Study Limitations
Tzoulaki 2009	Retrospective Cohort	UK general practice research database 1990-2005	RSG (8442+9640) 18,082 PIO 3,816 SU (6053+58,095) 64,148 MET 68,181 Other drugs or combinations 37,253	RSG mono vs. MET mono 0.97 (0.64-1.48)	-All cause mortality not well captured in GPRD
Vanasse 2009	Nested case-control	Ministrere de la santé et des Services Sociaux, Reigie de l'Assurance Maladie du Quebec 2001-2002	MI case 4 274 Controls 85 480	RSG currently exposed vs No TZD 1.41 (1.21-1.65)	-Short median follow-up of only 364 days - Reference group included patients not taking any anti-glycemic medications, representing about 50% of diabetic patients in the province of Quebec. - Comparing subjects exposed to RSG to those not exposed to anti-glycemic agents is not appropriate

Figure 19 Risk of MI Comparing RSG and Other Antidiabetic Agents



*RSG vs. SU
**RSG vs. MET
†SU=sulfonylurea, MET=MET
‡Note: Studies are ordered in ascending order of variance of risk ratios

Table 16 Studies Comparing the Risk of Myocardial Infarction in Rosiglitazone and Pioglitazone

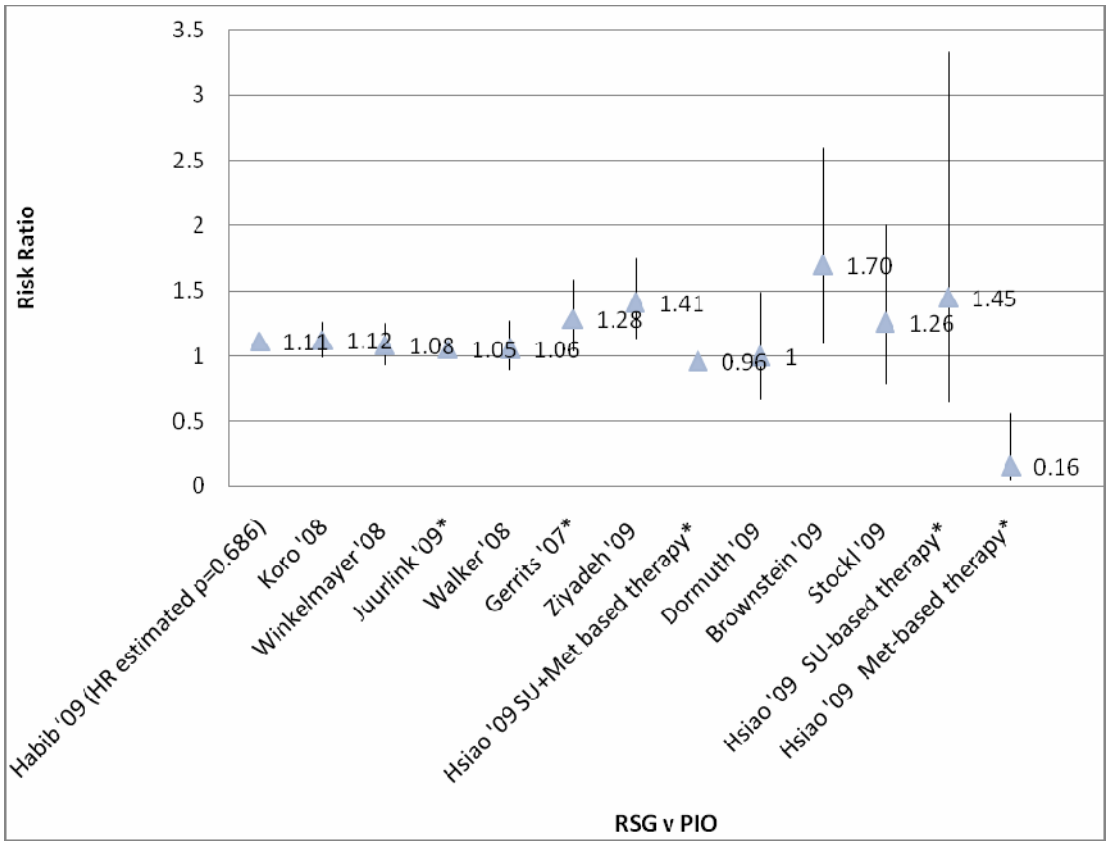
Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI) for MI*	Major Study Limitations
Gerrits 2007	Retrospective Cohort	Ingenix Research Database 2003-2006	RSG 14 807 PIO 15 104	PIO vs. RSG* 0.78 (0.63-0.96)	-CV risks different for PIO and RSG cohorts at baseline (MET use higher in RSG and statin/fibrate use higher in PIO) -Drug exposure described as time-varying, but analyzed as fixed
Koro 2008	Nested case-control	Integrated Healthcare information Services (IHCIS) 1999-2006	Diabetes cohort 891 901 MI cases 9 870 MI controls 29 610	RSG vs. PIO 1.12 (0.99-1.26)	-Potential for residual bias due to unmeasured predictors of MI (e.g., BMI, smoking status, duration of diabetes)
Walker 2008	Balanced Retrospective Cohort	Pharmetrics 2000-2007	RSG 57 381 PIO 51 641 Non-TZD 293 823	RSG vs. PIO 1.06 (0.89-1.27)	-Duration on a given anti-glycemic regimen short (average on treatment time <1 yr for all regimens)
Winkelmayer 2008	Retrospective Cohort	New Jersey Pharmaceutical Assistance for the Aged and Disabled program & Pennsylvania Pharmaceutical Assistance Contract for the Elderly program 2000-2005	RSG 14 101 PIO 14 260	RSG vs. PIO on-drug exposure 1.08 (0.93-1.25)** constant-exposure 1.01 (0.92-1.12) **primary analysis	-Baseline risk for cardiovascular disease may be higher for RSG group; RSG had more diagnosed coronary artery disease and congestive heart failure and less use of beta-blockers and statins -Ascertainment of mortality unclear - Only about a year of median or mean time of exposure to study drug
Brownstein 2010	Retrospective Cohort	Partners Healthcare System including Brigham and Women's and Massachusetts General Hospital Research Patient Data Registry 2000-2006	RSG 1 879 MET 12 490 SU 11 200 PIO 806	RSG vs. PIO 1.7 (1.1-2.6)	-Lack of complete prescription data for all individual patients -Low specificity for detection of myocardial infarction events (74%) -Low sample size for RSG exposed subjects
Dormuth 2009	Nested case-control study in prior MET	British Columbia databases (PharmaNet, BC Ministry	Case 2 244 Control 8 903	RSG vs. PIO (1-6 months) 1.41 (0.74-2.66)	-Small sample size for PIO group (use of PIO was half that of RSG)

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI) for MI*	Major Study Limitations
	users	of Health Database, Canadian Institute of Health Information) 2003-2007			
Habib 2009	Time-updated Propensity score adjusted cohort	Henry Ford A large vertically integrated health system 2000-2007	Entire Cohort 19 171 RSG 1 056 PIO 3 217	RSG vs. No TZD 1.00 (0.64-1.58) PIO vs. No TZD 0.90 (0.69-1.18) RSG vs. PIO estimated 1.11 (p=0.686)	-RSG and PIO groups might be different in important ways including a greater percentage of the RSG group having a history of various cardiovascular diseases compared to the PIO group -Short follow-up (293 days for RSG, 294 days for PIO). -Wide 95% CIs for RSG and TZDs -Results regarding PIO and CHF not consistent with labeled class effect of TZD -PIO group 3 times greater in size than RSG -Actual duration of exposure not known
Hsiao 2009	Population based Retrospective Cohort	Taiwan's National Health Insurance claims database 2000-2005	RSG mono 2 093 PIO mono 495 SU-based therapy 104 023 MET-based therapy 49 626 SU+MET-based therapy 317 246	PIO vs. RSG* SU-based therapy 0.69 (0.30-1.55) MET-based therapy 6.34 (1.80-22.31) SU+MET-based therapy 1.04 (0.73-1.47)	-Wide 95% CIs reflecting low precision of the risk ratio estimates -Small sample of RSG exposed patients; only 0.44% of the study sample was on RSG monotherapy. -A much greater proportion of the subjects in the RSG group had previous history of cardiovascular events (e.g. 6.59% of any CV events the year prior in RSG vs. 1.51-3.55% in non-TZD)
Juurlink 2009	Retrospective Cohort	Ontario Public Drug Benefit Program 2002-2008	RSG 22 785 PIO 16 951	PIO vs. RSG* 0.95 (0.81-1.11)	-A higher percentage of the RSG cohort had previous cardiovascular admissions and procedures with a longer duration of

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI) for MI*	Major Study Limitations
					diabetes. -Much larger cohort for RSG than the PIO cohort - Inappropriate dose comparison was made in which 8 mg of RSG was compared to 30 mg/45 mg of PIO -Failure to show a dose response relationship with the outcome of interest for RSG, putting the robustness of the conclusion in question
Stockl 2009	Nested case-control	Prescription Solutions 2002-2006	Case 1 681 Control 6 653	RSG vs. PIO 1.26 (0.79-2.00)	-AMI risk increased with recent RSG exposure but not with current exposure -Patients who died of AMI before reaching the hospital not captured
Ziyadeh 2009	Retrospective Cohort	Ingenix 2000-2007	RSG 47 501 PIO 47 501	RSG vs. PIO Regimen Switch 1.35 (1.12-1.62) Regimen Stop 1.41 (1.13-1.75)** **More conservative analysis	-Reported diagnoses may represent suspected conditions being ruled out rather than confirmed conditions

*Note that the risk ratios are comparing PIO to RSG, where RSG is the reference group. Other risk ratios are comparing RSG to PIO.

Figure 20 Risk of MI Comparing RSG and PIO



*Point estimate and 95% confidence interval published for PIO vs. RSG comparison. RSG vs. PIO estimates are presented in this figure for consistency.
**Note: Studies are ordered in ascending order of variance of risk ratios except for Habib et al. 2009, for which the HR was estimated.

Table 17 Studies Comparing the Risk of Other CV Outcomes in RSG and Other Anti-Glycemic Agents

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI)	Major Study Limitations
Lipscombe 2007	Nested case-control	Health databases from Ontario, Canada (Ontario Drug Benefit database, National Ambulatory Care Reporting System database, Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan database, Registered Persons Database, Ontario Diabetes Database) 2002-2006	TZD mono 229 TZD combination 1 463 Other OHA mono 57 177 Other OHA combination 30 076	Current RSG mono vs. Current other OHA combination CHF 1.98 (1.44-2.72)	- Disproportionately small number of TZD subjects; The number of subjects for the primary exposure of interest, TZD monotherapy, was 229 compared to other oral hypoglycemic agents monotherapy (N= 57,177). -Lack of internal validity because current users of monotherapy (who should be at the early stages of their diabetes) were at increased risk for acute myocardial infarction, whereas the TZD combination therapy (typically more advanced) were at lower risk.
McAfee 2007	Propensity Matched Retrospective Cohort	Ingenix Research Database 2000-2005	RSG 12 874 Non-TZD 20 489	RSG vs. Non-TZD MI/CR 0.93 (0.80-1.10) CR 0.94 (0.79-1.12)	-Statistical power limited by the rarity of the outcomes especially in the insulin combination cohorts
Margolis 2008	Retrospective Cohort	UK The Health Information Network (THIN) 2002-2006	RSG 7 282 PIO 2 244 Non-TZD Excluding insulin 77 719 Including insulin 93 932	RSG vs. non-RSG Serious ASCVD 0.6 (0.5- 0.6)	-Methodology of drug exposure classification unclear -Lack of standard comparison group -No adjustment for medications associated with CV outcomes -Completeness of recording of hospitalizations for various events not known given that this is a general practice database

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI)	Major Study Limitations
Walker 2008	Balanced Retrospective Cohort	Pharmetrics 2000-2007	RSG 57 381 PIO 51 641 Non-TZD 293 823	RSG vs. Non-RSG MI/CR 1.03 (0.95-1.11) CR 1.01 (0.93-1.10)	-Duration on a given anti-glycemic regimen short (average on treatment time <1 yr for all regimens)
Habib 2009	Time-updated propensity score adjusted cohort	Henry Ford A large vertically integrated health system 2000-2007	Entire Cohort 19 171 RSG 1 056 PIO 3 217	RSG vs. No RSG CHF 1.65 (1.25-2.19) CHD 1.22 (0.91-1.63)	-RSG and PIO groups might be different in important ways including a greater percentage of the RSG group having a history of various cardiovascular diseases compared to the PIO group -Short follow-up (293 days for RSG, 294 days for PIO). -Wide 95% CIs for RSG and TZDs -Results regarding PIO and CHF not consistent with labeled class effect of TZD -PIO group 3 times greater in size than RSG -Actual duration of exposure not known
Hsiao 2009	Population based retrospective cohort	Taiwan's National Health Insurance Claims database 2000-2005	RSG mono 2 093 PIO mono 495 SU-based therapy 104 023 MET-based therapy 49 626 SU+MET-based therapy 317 246	RSG vs. SU CHF 1.22 (0.86-1.74) RSG vs. MET CHF 1.30 (0.89-1.89)	-Wide 95% CIs reflecting low precision of the risk ratio estimates -Small sample of RSG exposed patients; only 0.44% of the study sample was on RSG monotherapy. -A much greater proportion of the subjects in the RSG group had previous history of cardiovascular events (e.g. 6.59% of any CV events in the year prior in RSG vs. 1.51-3.55% in non-TZD)
Pantalone 2009	Retrospective Cohort	Electronic health record 1998-2006	RSG 1 079 MET 10 436 SU 7 427 PIO 1 508	RSG vs. SU CAD 0.90 (0.71-1.14) CHF 0.88 (0.60-1.31) RSG vs. MET CAD 0.96 (0.76-1.21)	-Exposure group defined at baseline; did not take into account stopping/switching/addition of other agents -Study groups not balanced with respect to baseline variables and risk factors -Accuracy of CAD

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI)	Major Study Limitations
				CHF 1.16 (0.78-1.73)	and CHF capture may be questionable
Ramirez 2009	Retrospective Cohort	Dialysis Outcomes and Practice Patterns Study I and II in US 1999-2004	RSG 177 PIO 118 Non-TZD OHA 2 050	<u>RSG vs. Non-TZD OHAs</u> CHF 1.21 (0.72-2.05) Cardiovascular mortality 1.59 (1.14-2.22)	- Small number of RSG exposed subject (N=177) representing only 7% of the study population - Missing data on the type of oral hypoglycemic agents for 47% of patients included in the study. -Significantly higher mean plasma glucose level for RSG patients at baseline compared to non-TZD oral hypoglycemic agents -RSG patients may have diabetes that is more difficult to control and carries a higher risk of cardiovascular outcomes.
Shaya 2009	Retrospective cohort	Maryland Medicaid medical encounter and prescription data from all managed care organizations in the state 2001-2006	TZD 5712 OAD 8911	<u>RSG vs. Other OADs</u> MI/stroke 1.124 (1.010-1.250)	-Limited generalizability; study population is a high risk, largely underrepresented and largely minority Medicaid population. -Conclusions are suspect given that in this study obesity in this study is a CV protective factor
Tzoulaki 2009	Retrospective Cohort	UK general practice research database 1990-2005	RSG (8442+9640) 18,082 PIO 3,816 SU (6053+58,095) 64,148 MET 68,181 Other drugs or combinations 37,253	<u>RSG mono vs. MET mono</u> First CHF 1.07 (0.77-1.48)	-All cause mortality not well captured in GPRD
Vanasse 2009	Nested case-control	Ministrere de la santé et des Services Sociaux, Reigie de l'Assurance Maladie du Quebec	Cohort 154 787 RSG 10 911	<u>RSG currently exposed vs. No TZD</u> CHF 1.94 (1.71-2.19) CV death 0.88 (0.69-1.12)	-Short median follow-up of only 364 days - Reference group included patients not taking any anti-glycemic medications, representing about 50% of diabetic patients in the province of

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI)	Major Study Limitations
		2001-2002			Quebec - Comparing subjects exposed to RSG to those not exposed to anti-glycemic agents is not appropriate

Table 18 Studies Comparing the Risk of Other CV Outcomes in RSG and Pioglitazone

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI)	Major Study Limitations
Gerrits 2007	Retrospective Cohort	Ingenix Research Database 2003-2006	RSG 14 807 PIO 15 104	PIO vs. RSG* MI/CR 0.85 (0.75-0.98)	-CV risks different for PIO and RSG cohorts at baseline (MET use higher in RSG and statin/fibrate use higher in PIO) -Drug exposure described as time-varying, but analyzed as fixed
Margolis 2008	Retrospective Cohort	UK The Health Information Network (THIN) 2002-2006	RSG 7 282 PIO 2 244 Non-TZD Excluding insulin 77 719 Including insulin 93 932	RSG vs. PIO ASCVD 1.0 (0.8-1.3)	-Methodology of drug exposure classification unclear -Lack of standard comparison group -No adjustment for medications associated with CV outcomes -Completeness of recording of hospitalizations for various events not known given that this is a general practice database
Walker 2008	Balanced Retrospective Cohort	Pharmetrics 2000-2007	RSG 57 381 PIO 51 641 Non-TZD 293 823	RSG vs. PIO MI/CR 1.04 (0.94-1.14) CR 1.03 (0.93-1.14)	-Duration on a given anti-glycemic regimen short (average on treatment time <1 yr for all regimens)
Winkelmayer 2008	Retrospective Cohort	New Jersey Pharmaceutical Assistance for the Aged and Disabled program & Pennsylvania Pharmaceutical Assistance Contract for the Elderly program 2000-2005	RSG 14 101 PIO 14 260	RSG vs. PIO (on-drug exposure) CHF 1.13 (1.01-1.26)** RSG vs. PIO (constant-exposure) CHF 1.11 (1.03-1.19) **primary analysis	-Baseline risk for cardiovascular disease may be higher for RSG group; RSG had more diagnosed coronary artery disease and congestive heart failure and less use of beta-blockers and statins -Ascertainment of mortality unclear - Only about a year of median or mean time of exposure to study drug
Habib 2009	Time-updated propensity score adjusted cohort	Henry Ford A large vertically integrated health system 2000-2007	Entire Cohort 19 171 RSG 1 056 PIO 3 217	HR for CHF RSG vs. No TZD 1.66 (1.28-2.15) PIO vs. No TZD 1.13 (0.95-1.34) RSG vs. PIO estimated 1.47 (p=0.013)	-RSG and PIO groups might be different in important ways including a greater percentage of the RSG group having a history of various cardiovascular diseases

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI)	Major Study Limitations
				HR for CHD RSG vs. No TZD 1.22 (0.89-1.67) PIO vs. No TZD 0.84 (0.69-1.04) RSG vs. PIO estimated 1.45 (p=0.048)	compared to the PIO group -Short follow-up (293 days for RSG, 294 days for PIO). -Wide 95% CIs for RSG and TZDs -Results regarding PIO and CHF not consistent with labeled class effect of TZD -PIO group 3 times greater in size than RSG -Actual duration of exposure not known
Hsiao 2009	Population based retrospective cohort	Taiwan's National Health Insurance Claims database 2000-2005	RSG mono 2 093 PIO mono 495 SU-based therapy 104 023 MET-based therapy 49 626 SU+MET-based therapy 317 246	PIO vs. RSG* (SU-based therapy) CHF 0.78 (0.36-1.69) PIO vs. RSG* (MET-based therapy) CHF 0.63 (0.14-2.82) PIO vs. RSG* (SU+MET-based therapy) CHF 1.06 (0.78-1.44)	-Wide 95% CIs reflecting low precision of the risk ratio estimates -Small sample of RSG exposed patients; only 0.44% of the study sample was on RSG monotherapy. -A much greater proportion of the subjects in the RSG group had previous history of cardiovascular events (e.g. 6.59% of any CV events in the year prior in RSG vs. 1.51-3.55% in non-TZD)
Juurlink 2009	Cohort	Ontario Public Drug Benefit Program 2002-2008	RSG 22 785 PIO 16 951	PIO vs. RSG* Heart failure 0.77 (0.69-0.87)	-A higher percentage of the RSG cohort had previous cardiovascular admissions and procedures with a longer duration of diabetes. -Much larger cohort for RSG than the PIO cohort - Inappropriate dose comparison was made in which 8 mg of RSG was compared to 30 mg/45 mg of PIO -Failure to show a dose response relationship with the outcome of interest for RSG, putting the robustness of the conclusion in question
Pantalone 2009	Cohort	Electronic health record 1998-2006	RSG 1 079 MET	PIO vs. RSG* CAD 1.15 (0.87-1.53)	-Exposure group defined at baseline; did not take into account

Author Year	Study Design	Data Source Time Period	Sample Size	Risk Ratio (95% CI)	Major Study Limitations
			10 436 SU 7 427 PIO 1 508	CHF 1.19 (0.74-1.91)	stopping/switching/addition of other agents -Study groups not balanced with respect to baseline variables and risk factors -Accuracy of CAD and CHF capture may be questionable
Ziyadeh 2009	Cohort	Ingenix 2000-2007	RSG 47 501 PIO 47 501	<u>RSG vs. PIO (Regimen Switch)</u> CR 1.08 (0.95-1.22) MI/CR 1.10 (0.98-1.23) MI/CR/Sudden death 1.09 (0.97-1.22) <u>RSG vs. PIO (Regimen Stop)</u> CR 1.12 (0.98-1.29)** MI/CR 1.12 (0.99-1.28)** MI/CR/Sudden death 1.12 (0.98-1.27)** **More conservative analysis	-Reported diagnoses may represent suspected conditions being ruled out rather than confirmed conditions

*Note that the risk ratios are comparing PIO to RSG, where RSG is the reference group. Other risk ratios are comparing RSG to PIO.

9.4. Appendix 4. RECORD- Final Results, Home 2009

Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial

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Summary

Background Rosiglitazone is an insulin sensitiser used in combination with metformin, a sulfonylurea, or both, for lowering blood glucose in people with type 2 diabetes. We assessed cardiovascular outcomes after addition of rosiglitazone to either metformin or sulfonylurea compared with the combination of the two over 5–7 years of follow-up. We also assessed comparative safety.

Methods In a multicentre, open-label trial, 4447 patients with type 2 diabetes on metformin or sulfonylurea monotherapy with mean haemoglobin A_{1c} (HbA_{1c}) of 7·9% were randomly assigned to addition of rosiglitazone (n=2220) or to a combination of metformin and sulfonylurea (active control group, n=2227). The primary endpoint was cardiovascular hospitalisation or cardiovascular death, with a hazard ratio (HR) non-inferiority margin of 1·20. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00379769.

Findings 321 people in the rosiglitazone group and 323 in the active control group experienced the primary outcome during a mean 5·5-year follow-up, meeting the criterion of non-inferiority (HR 0·99, 95% CI 0·85–1·16). HR was 0·84 (0·59–1·18) for cardiovascular death, 1·14 (0·80–1·63) for myocardial infarction, and 0·72 (0·49–1·06) for stroke. Heart failure causing admission to hospital or death occurred in 61 people in the rosiglitazone group and 29 in the active control group (HR 2·10, 1·35–3·27, risk difference per 1000 person-years 2·6, 1·1–4·1). Upper and distal lower limb fracture rates were increased mainly in women randomly assigned to rosiglitazone. Mean HbA_{1c} was lower in the rosiglitazone group than in the control group at 5 years.

Interpretation Addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes is confirmed to increase the risk of heart failure and of some fractures, mainly in women. Although the data are inconclusive about any possible effect on myocardial infarction, rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs.

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Introduction

Individual oral glucose-lowering medications have limited efficacy,[1–3] and hence are commonly used in combination.[4] In 2000, the thiazolidinediones rosiglitazone and pioglitazone received marketing authorisation for use in combination with metformin and sulfonylureas in Europe. These thiazolidinediones were known to cause fluid retention and possibly heart failure, and both manufacturers were requested to undertake a post-marketing cardiovascular outcome study.[5,6]

From data reported in the UK Prospective Diabetes Study (UKPDS) in 1998, metformin seemed to protect against cardiovascular risk, but uncertainty remained for sulfonylureas.[1,7] After 1999, evidence showed that thiazolidinediones improved some cardiovascular risk markers associated with diabetes—including insulin sensitivity, blood pressure, and coagulation factors.[2,8,9] However, higher LDL cholesterol concentrations, albeit in the context of improvement in LDL phenotype and unchanged LDL to HDL cholesterol ratio,[10] raised concern about the overall cardiovascular effect of rosiglitazone.

Concerns increased because several peroxisome proliferator-activated receptor (PPAR) αγ agonists failed in development as a result of cardiovascular problems in humans or malignancy, in particular bladder tumours, in animals.[11] The PROactive secondary prevention study of the PPARαγ agonist pioglitazone was inconclusive for its primary composite cardiovascular endpoint, but showed a reduction for the secondary composite of death, myocardial infarction, and stroke compared with placebo.[12]

For rosiglitazone, which is a PPARγ agonist, an active-comparator cardiovascular outcome study (RECORD) was designed from the time of marketing authorisation.[13] In 2006, the manufacturer (GlaxoSmithKline) submitted to drug regulators a combined analysis of several studies which suggested that, despite large observational studies to the contrary,[14,15] rosiglitazone increased myocardial ischaemia.[16] Nissen and Wolski, using similar data sources, reached similar conclusions.[17] The RECORD steering committee published an unplanned interim analysis at that time.[18]

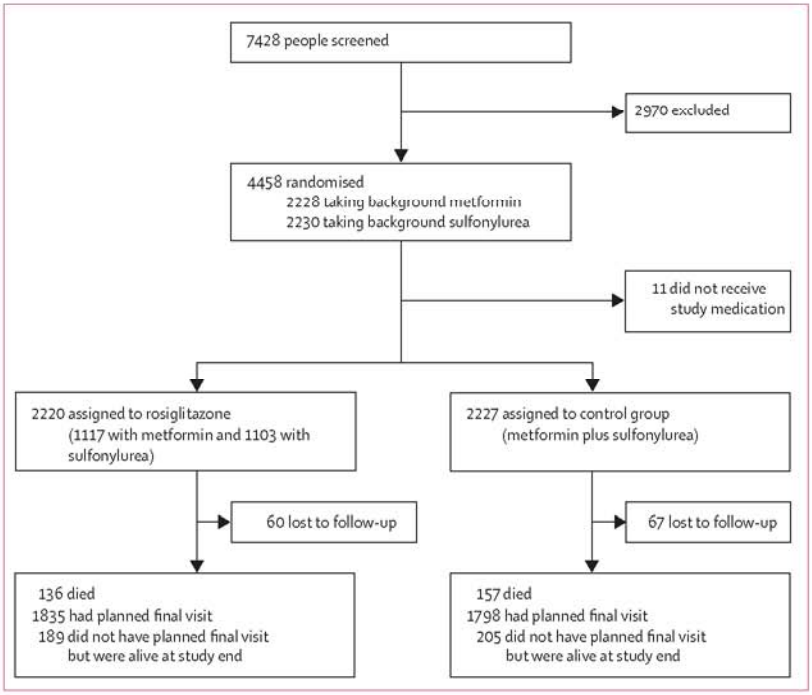

Figure 1: Trial profile

Here, we report the final planned analysis of the RECORD trial, with 7935 (48%) more person-years of follow-up than at interim analysis, and we focus mainly on protocol-defined cardiovascular outcomes. Furthermore, accumulation of around 25 000 person-years of follow-up provides the opportunity to address, through adverse-event reporting, concern over malignancy[11] and the issue of limb fractures raised by the ADOPT study.[19]

Our aim was to assess non-inferiority of rosiglitazone in combination with metformin or sulfonylurea compared with metformin and sulfonylurea dual therapy for cardiovascular outcomes. The primary endpoint was the time to first cardiovascular hospitalisation or cardiovascular death.

Methods

Study design

RECORD was a prospective, multicentre, randomised, open-label trial of dual therapy in patients with type 2 diabetes, comparing rosiglitazone plus either metformin or a sulfonylurea with an active control, metformin plus a sulfonylurea. The study design has been described in detail previously.[13,18] Patients with type 2 diabetes on monotherapy with either metformin or sulfonylurea and in less than optimal blood glucose control (haemoglobin A_{1c} [HbA_{1c}] >7·0–9·0%) were randomly assigned to addition of rosiglitazone or metformin (if already on sulfonylurea) or of rosiglitazone or sulfonylurea (if already on metformin). Data for glucose control and ambulatory blood pressure have already been published,[2,9] as was an interim analysis forced by controversy over cardiovascular risk.[18]

The study was done in 364 centres in 25 countries in Europe and Australasia. Randomisation was by telephone from a dedicated centre, using random-permuted blocks stratified by background medication. The study was open label because of planned differences in the strategy for rescue therapy and the need to allow different types and doses of comparator sulfonylurea therapy. Choice of sulfonylurea (glimepiride, gliclazide, or glibenclamide [glyburide]) was according to local investigator practice. Other glucose-lowering therapies were not permitted.

The study was monitored by a clinical trials organisation (Quintiles, Bracknell, UK), which also coordinated data collection. Biochemical measurements were done by a central laboratory (Quest Diagnostics, Heston, UK). The study was overseen by a steering committee. An independent data safety and monitoring board reviewed conduct of the study and unblinded data at about 6-month intervals. Interim analyses were not made available to the steering committee, except for those required for the interim publication.[18] Adverse-event data were made available to the pharmacovigilance department of the sponsor, but not to staff involved with the study.

Patients

Eligibility criteria have been detailed previously.[13] Requirements were: age between 40 and 75 years, body-mass index of more than 25·0 kg/m², and being on maximum tolerated doses of metformin or a sulfonylurea monotherapy. Exclusions included hospitalisation for a major cardiovascular event in the 3 months before the trial, planned cardiovascular intervention, and presence, history, or treatment for heart failure. Written informed consent was obtained from each participant.[13] Recruitment was from April, 2001, to April, 2003, and last study visits were from August to December, 2008.

Treatments

Oral glucose-lowering therapies were managed throughout to a target HbA_{1c} of 7·0% or less. Rosiglitazone (Avandia, GlaxoSmithKline, UK) was begun at 4 mg per day, and titrated to 8 mg any time after 8 weeks of therapy, if not to target. The starting dose of metformin and sulfonylurea varied by local practice, with dose increases permitted from 8 weeks after beginning of therapy. Maximum daily doses of 2550 mg metformin, 15 mg glibenclamide (or equivalent for different preparations), 240 mg gliclazide, or 4 mg glimepiride were stipulated.[20] The criterion for rescue therapy by addition of a third oral agent (if in the rosiglitazone group) or transfer to insulin (in the metformin plus sulfonylurea group) was a confirmed HbA_{1c} of 8·5% or more. Subsequently, if participants taking triple therapy (with rosiglitazone) had a confirmed HbA_{1c} of 8·5% or more, rosiglitazone was to be stopped and insulin therapy substituted.

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Outcome measures and adverse events

The primary outcome was time to first occurrence of cardiovascular hospitalisation or cardiovascular death. The primary hypothesis to be tested was non-inferiority of rosiglitazone compared with active control with a prespecified non-inferiority margin of 1·20 for the hazard ratio (HR). Therefore, if the upper limit of the CI of the HR was less than 1·20, non-inferiority could be claimed.

Some sensitivity analyses on the primary endpoint were predefined, including one with non-atherosclerotic events removed (ie, pacemaker insertion, cardiac conducting tissue ablation, bradycardia, deep venous thrombosis, pericarditis, cardiac surgery complications, pulmonary embolism, syncope, valve surgery or valvular heart disease, hypertensive emergency, and subdural haematoma).

Deaths and investigator-diagnosed cardiovascular events were identified through adverse-event reporting, direct questioning, or both, at study visits with trial record forms. Data from all relevant clinical sources were obtained by Quintiles and provided to an independent clinical endpoints committee who were blind to treatment allocation. All deaths were adjudicated with predefined criteria. Cardiovascular deaths included those with a definite cardiovascular cause and those of unknown cause. Cardiovascular hospitalisations included any acute or unplanned admission for a cardiovascular reason—such as heart failure, transient ischaemic attack, thrombotic events, unplanned cardiovascular revascularisations, and amputation of extremities—in addition to traditional cardiovascular emergencies, such as acute myocardial infarction or stroke. In a sensitivity analysis, cardiovascular deaths adjudicated as of unknown cause were reattributed according to investigator opinion.

Adverse events and serious adverse events were obtained for all participants while on dual or triple oral therapy, and serious adverse events thereafter. After publication of the ADOPT study,[19] fracture events were also obtained by direct questioning at study visits.

	Background metformin		Background sulfonylurea	
	Rosiglitazone (N=1117)	Sulfonylurea (N=1105)	Rosiglitazone (N=1103)	Metformin (N=1122)
Age (years)	57·0 (8·0)	57·2 (8·1)	59·8 (8·3)	59·7 (8·2)
Sex (male)	601 (53·8%)	584 (52·9%)	541 (49·0%)	568 (50·6%)
Ethnic origin (white)	1105 (98·9%)	1087 (98·4%)	1095 (99·3%)	1112 (99·1%)
Ischaemic heart disease	171 (15·3%)	164 (14·8%)	212 (19·2%)	225 (20·1%)
Stable angina	105 (9·4%)	86 (7·8%)	122 (11·1%)	144 (12·8%)
Myocardial infarction	50 (4·5%)	62 (5·6%)	54 (4·9%)	52 (4·6%)
Stroke	26 (2·3%)	20 (1·8%)	29 (2·6%)	33 (2·9%)
Transient ischaemic attack	27 (2·4%)	25 (2·3%)	24 (2·2%)	22 (2·0%)
Peripheral arterial disease	80 (7·2%)	96 (8·7%)	117 (10·6%)	117 (10·4%)
Heart failure	4 (0·4%)	4 (0·4%)	8 (0·7%)	5 (0·4%)
Retinopathy	73 (6·5%)	77 (7·0%)	141 (12·8%)	157 (14·0%)
Current smoker	199 (17·8%)	194 (17·6%)	164 (14·9%)	149 (13·3%)
Microalbuminuria or proteinuria*	225 (20·1%)	192 (17·4%)	215 (19·5%)	219 (19·5%)
Duration from diabetes diagnosis (years)	6·1 (4·2)	6·3 (4·4)	7·9 (5·5)	7·9 (5·2)
Weight (kg)	93·5 (16·5)	93·3 (16·3)	85·0 (14·5)	84·3 (14·4)
Body-mass index (kg/m^2)	32·8 (5·0)	32·7 (5·2)	30·3 (4·1)	30·1 (4·3)
HbA_{1c} (%)	7·8 (0·7)	7·8 (0·7)	8·0 (0·7)	8·0 (0·7)
Fasting plasma glucose (mmol/L)	9·5 (2·1)	9·5 (2·1)	10·2 (2·6)	10·1 (2·3)
Systolic blood pressure (mm Hg)	140 (16)	139 (16)	138 (15)	138 (15)
Diastolic blood pressure (mm Hg)	84 (9)	83 (9)	82 (8)	82 (8)
Heart rate (beat/min)	74 (9)	74 (9)	73 (9)	74 (9)
LDL cholesterol (mmol/L)	3·2 (0·9)	3·2 (0·9)	3·4 (0·9)	3·4 (0·9)
HDL cholesterol (mmol/L)	1·2 (0·3)	1·2 (0·3)	1·2 (0·3)	1·2 (0·3)
Triglyceride (mmol/L)	2·3 (1·3)	2·4 (1·5)	2·3 (1·7)	2·2 (1·6)
Serum creatinine (μmol/L)	63·7 (16·1)	64·5 (21·1)	65·3 (16·3)	65·3 (16·5)

Data are number (%) or mean (SD). HbA_{1c}=haemoglobin A_{1c}. *Microalbuminuria is defined as albumin to creatinine ratio >2·5 mg/mmol (men) or >3·5 mg/mmol (women).

Table 1: **Baseline characteristics of the people with diabetes studied, divided by background treatment stratum and randomised therapy group**

Statistical analysis

For the non-inferiority hypothesis, 4000 participants followed for a median time of 6 years were needed to give 99% power, provided that the active control group had an 11% event rate per year, allowing 2% annual loss to follow-up. Blinded overall event tracking showed the event rate during the study was well below this rate. Therefore, endpoint sweeps were implemented to identify any missed events. An in-depth review of a sample of individual records showed very few missed events.

The hypothesis of non-inferiority for the primary endpoint was tested on the randomised and treated population, using analysis by intention to treat. A sensitivity per-protocol analysis was restricted to each participant's time on dual combination therapy plus 30 days thereafter. Time from randomisation to first defined event was calculated for each relevant event. The comparison between the rosiglitazone group and the control group was estimated as an HR (with 95% CI) on the basis of Cox proportional hazards regression stratified for background medication. Two-sided p values were derived from the asymptotic Wald tests, unadjusted for multiple testing. Cumulative incidence was estimated with the Kaplan-Meier method. Event rates were calculated according to individual time in study by randomisation group, without censoring for rescue therapy, and enabled calculation of absolute risk differences.

Analyses of changes in HbA_{1c} and other quantitative measures at 5 years used a repeated measures model (based on all available data and assuming data were missing at random), including terms for baseline and baseline by visit interaction, with an unstructured covariance matrix for the within-patient variability in each treatment group. Incidence of adverse-event data was compared using a stratified Fisher's exact test.

The statistical analysis was done by the sponsor's statisticians according to a detailed predefined statistical

	Background metformin			Background sulfonylurea		
	Rosiglitazone	Sulfonylurea	p	Rosiglitazone	Metformin	p
HbA_{1c} (%)	−0·28 (0·03)	0·01 (0·04)	<0·0001	−0·44 (0·03)	−0·18 (0·04)	<0·0001
LDL cholesterol (mmol/L)†	−0·33 (0·04)	−0·50 (0·03)	0·0001	−0·22 (0·04)	−0·53 (0·03)	<0·0001
HDL cholesterol (mmol/L)†	0·12 (0·01)	0·04 (0·01)	<0·0001	0·11 (0·01)	0·07 (0·01)	0·002
Triglycerides (mmol/L)†	−0·14 (0·04)	−0·02 (0·05)	0·046	−0·13 (0·04)	−0·14 (0·04)	0·82
Weight (kg)	3·8 (0·24)	0·0 (0·2)	<0·0001	4·1 (0·2)	−1·5 (0·2)	<0·0001
Blood pressure (mm Hg)						
Systolic	−1·5 (0·5)	−2·2 (0·5)	0·31	−1·5 (0·5)	−0·9 (0·5)	0·34
Diastolic	−3·6 (0·3)	−3·4 (0·3)	0·72	−3·1 (0·3)	−2·4 (0·3)	0·060

Data are mean (SE). HbA_{1c}=haemoglobin A_{1c}. *Estimates of 5-year changes obtained with a baseline-adjusted repeated-measures model for all patient data (and p values for treatment difference). †Lipids were not measured after initiation of any insulin therapy.

Table 2: **Mean change in cardiovascular risk factors from baseline to 5-year follow-up***

	Rosiglitazone		Active control	
	Baseline (N=2220)	At 5 years (N=1918)	Baseline (N=2227)	At 5 years (N=1892)
Statins	400 (18·0%)	1059 (55·2%)	428 (19·2%)	871 (46·0%)
Fibrates	131 (5·9%)	211 (11·0%)	121 (5·4%)	203 (10·7%)
Thiazide diuretics	209 (9·4%)	411 (21·4%)	225 (10·1%)	368 (19·5%)
Loop diuretics	69 (3·1%)	250 (13·0%)	68 (3·1%)	153 (8·1%)
β-adrenergic blockers	501 (22·6%)	716 (37·3%)	465 (20·9%)	700 (37·0%)
ACE inhibitors/A2R blockers	957 (43·1%)	1196 (62·4%)	937 (42·1%)	1216 (64·3%)
Calcium channel blockers	424 (19·1%)	615 (32·1%)	481 (21·6%)	685 (36·2%)
Nitrates	132 (5·9%)	196 (10·2%)	140 (6·3%)	200 (10·6%)
Antiplatelet agents	445 (20·0%)	683 (35·6%)	422 (18·9%)	689 (36·4%)

Data are number (%). ACE=angiotensin-converting enzyme. A2R=angiotensin 2 receptor.

Table 3: **Concomitant cardiovascular medications at baseline and at 5 years**

analysis plan agreed by the steering committee, with SAS software version 8.2 (Cary, NC, USA). Confirmatory analyses were done by an independent investigator (London School of Hygiene and Tropical Medicine, UK) with SAS software. This study is registered with ClinicalTrials.gov, number NCT00379769.

Role of the funding source

The sponsor of the study was GlaxoSmithKline (Brentford, UK). Sponsor statisticians were involved in the design, reporting plan, and data analysis. The steering committee had responsibility for study conduct, data collected, data analysis, the writing of this report, and the decision to publish.

Results

Of 7428 patients screened, 4458 were randomly allocated to study groups (figure 1). 11 did not take study medication and were excluded from analysis. 2222 people on metformin were assigned to addition of rosiglitazone (1117) or sulfonylurea (1105), and 2225 patients on a sulfonylurea were assigned to addition of rosiglitazone (1103) or metformin (1122). Mean follow-up duration was 5·5 years, which corresponded to 12 338 person-years in the rosiglitazone group and 12 272 person-years in the comparator group. Vital status was unknown at study end in 127 people (2·9%, 60 rosiglitazone and 67 control), and a further 394 were alive but withdrew from some study visits, thereby missing complete cardiovascular endpoint information (8·9%, 189 rosiglitazone and 205 control). In the 12 months after May 20, 2007 (the time of publication of the report by Nissen and Wolski[17]), discontinuations from rosiglitazone therapy increased slightly compared with those in the active control group. This increase amounted to an excess of 32 people (1·4% of the randomised population) withdrawn from randomised treatment.

Baseline characteristics between randomisation groups were similar (table 1). In the background metformin stratum, people were younger, more obese, and had a shorter duration from diabetes diagnosis than those in the background sulfonylurea stratum (table 1).

Mean HbA_{1c} at 5 years was lowered more in people randomly assigned to rosiglitazone, whereas bodyweight and HDL cholesterol increased more, and LDL cholesterol was reduced less, than in the groups randomly assigned to either sulfonylurea or metformin (table 2). In the rosiglitazone group, 75% of person-years' follow-up were on dual oral therapy and 13% on triple oral therapy. In the control group, 83% of person-years' follow-up were on dual oral therapy. Use of concomitant cardiovascular-related medications had risen greatly by 5 years for both rosiglitazone and active control groups (table 3). Use of statins was significantly greater (9·2%) at 5 years in the rosiglitazone group than in the control group; this was also the case for loop diuretics (4·9%).

Table 4 shows the numbers of people affected, HR, risk difference, CIs, and p values for the main cardiovascular outcomes. Kaplan-Meier plots are in figures 2 and 3. The event rate was 28 per 1000 person-years for the primary endpoint. The primary endpoint (cardiovascular hospitalisation or cardiovascular death) occurred in 321 and 323 participants assigned to the rosiglitazone and active control groups, respectively (HR 0·99, 95% CI 0·85–1·16). The

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prespecified criterion of non-inferiority was met (table 4). A prespecified sensitivity analysis excluding some cardiovascular events not of atherosclerotic origin gave similar results (HR 0·97, 0·82–1·14). A per-protocol analysis excluding any participant 30 days after transfer from dual therapy gave similar results (HR 1·02, 0·85–1·21): cardiovascular deaths or hospitalisations were 240 on rosiglitazone and 260 on active control, with exposures of 8905 and 9818 person-years, respectively. Within-strata comparisons of those randomly assigned to rosiglitazone with those randomly assigned to metformin (HR 0·98, 0·79–1·21) or to sulfonylureas (HR 1·01, 0·81–1·26) gave similar results, with no evidence of between-strata interaction (p=0·84).

Cardiovascular deaths and all-cause deaths were fewer in the rosiglitazone group than in the control group, but not significantly different (table 4). HRs for myocardial infarction and stroke were slightly but not significantly different. The predefined composite secondary endpoint of cardiovascular death, myocardial infarction, and stroke gave an HR of 0·93 (0·74–1·15) for rosiglitazone against active comparator. A broader composite also including heart failure and unstable angina gave an HR of 0·99 (0·81–1·20). The rate of heart failure approximately doubled in the rosiglitazone group compared with that in the control group (table 4).

Table 5 shows the types of cardiovascular death and hospitalisation by treatment group. For cardiovascular mortality, the rosiglitazone group had more heart-failure-related deaths but fewer stroke-related deaths and other vascular deaths than had the active control group. A sensitivity analysis using investigator opinion to attribute cause to deaths adjudicated as of unknown aetiology did not affect the findings. Total cardiovascular hospitalisations were almost equal in the two groups: the rosiglitazone group had more heart-failure hospitalisations, fewer stroke hospitalisations, and fewer cardiovascular procedures than had the active control group.

Prespecified subgroup analyses on the primary endpoint showed consistent findings for the randomised comparison for participants subdivided by baseline characteristics (figure 4). Only for patients with previous history of ischaemic heart disease (yes or no) was there a suggestion of heterogeneity (interaction p=0·055), whereby more primary endpoints seem to be present for those with previous ischaemic heart disease in the rosiglitazone group than in the active comparator group (figure 4).

Although the incidence of heart failure was higher in the rosiglitazone group for people both with and without previous ischaemic heart disease, other reasons for cardiovascular hospitalisation or death showed no evidence of such excess. Specifically, the number of cases with heart failure with and without previous ischaemic heart disease were 17 (rosiglitazone) versus 8 (control) and 44 (rosiglitazone) versus 21 (control), giving similar relative risks (2·16 and 2·10) in these two subgroups. For people allocated to rosiglitazone, the presence of baseline stable angina or previous myocardial infarction carried no increased risk for a primary endpoint event (rosiglitazone 59 *vs* control 56 and 37 *vs* 35 events).

Table 6 summarises the rate of investigator-reported serious adverse events in more than 20 people or of events of particular interest in the context of PPAR agonists. Heart failure was significantly higher in people treated with rosiglitazone than in those treated with the active control. However, myocardial infarction did not differ between groups, whereas stroke might have been less frequent in people treated with rosiglitazone than in those treated with the active control (table 6). Overall incidence of malignancy or of some tumour types including bladder and colon cancer did not differ in the two groups, but pancreatic cancer was less frequently reported in the rosiglitazone group than in the active control group (table 6).

	Rosiglitazone (N=2220)	Active control (N=2227)	HR	Rate difference per 1000 person-years	p
CV death or CV hospitalisation	321	323	0·99 (0·85 to 1·16)	−0·2 (−4·5 to 4·1)	0·93
All-cause death	136	157	0·86 (0·68 to 1·08)	−1·7 (−4·3 to 0·9)	0·19
CV death	60	71	0·84 (0·59 to 1·18)	−0·9 (−2·7 to 0·9)	0·32
Myocardial infarction*	64	56	1·14 (0·80 to 1·63)	0·6 (−1·1 to 2·4)	0·47
Stroke*	46	63	0·72 (0·49 to 1·06)	−1·4 (−3·1 to 0·2)	0·10
CV death, MI, or stroke	154	165	0·93 (0·74 to 1·15)	−1·0 (−3·9 to 1·9)	0·50
Heart failure*	61	29	2·10 (1·35 to 3·27)	2·6 (1·1 to 4·1)	0·0010

Data are numbers, HR (95% CI), or rate differences (95% CI). CV=cardiovascular. MI=myocardial infarction. *Fatal and non-fatal.

Table 4: **Deaths and hospitalisations from cardiovascular causes**

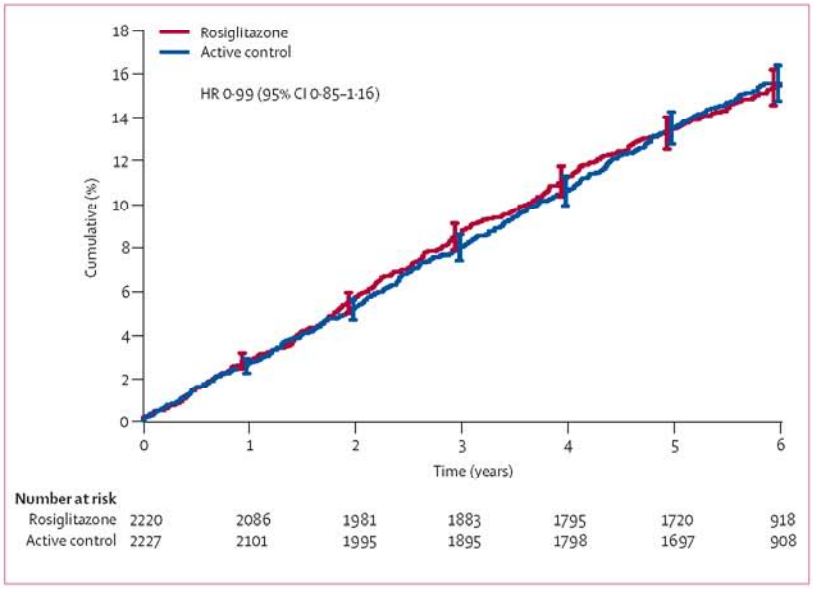

Figure 2: **Kaplan-Meier plots of time to the primary endpoint (cardiovascular death or cardiovascular hospitalisation)**
HR=hazard ratio.

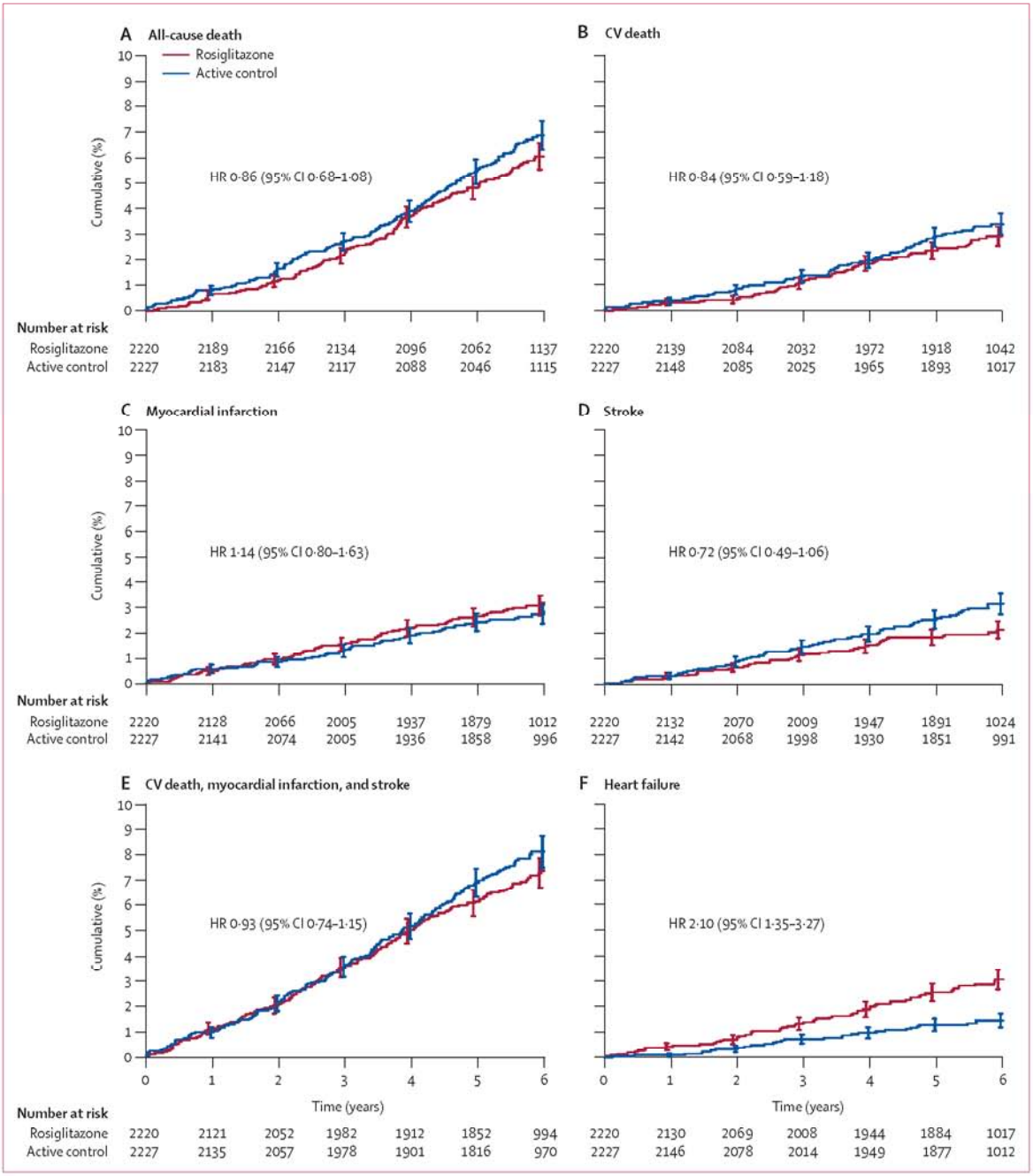

Figure 3: **Kaplan-Meier plots for components of the primary endpoint**
(A) All-cause death. (B) CV death. (C) Myocardial infarction. (D) Stroke. (E) CV death, myocardial infarction, and stroke. (F) Heart failure. CV=cardiovascular. HR=hazard ratio.

Serious adverse events due to hyperglycaemia were less frequent, and those due to hypoglycaemia more frequent, in the rosiglitazone group than in the control group (table 6). The incidence of all adverse events due to hypoglycaemia (serious and non-serious) was higher in the sulfonylurea-containing groups (sulfonylurea added to metformin [197 patients, 18%], metformin added to sulfonylurea [148, 13%], and rosiglitazone added to sulfonylurea [175, 16%]) than when rosiglitazone was added to metformin (57 patients, 5%). There were no serious adverse-event reports of macular oedema. Non-serious adverse-event reports of macular oedema in people on rosiglitazone were seven, and three in people on the active control.

The overall incidence of participant-reported bone fractures was higher in the rosiglitazone group than in

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the active control group (risk ratio [RR] 1·57, 95% CI 1·26–1·97, p<0·0001) (table 7). The RR seemed to be higher in women than in men (1·82, 1·37–2·41 *vs* 1·23, 0·85–1·77; interaction p=0·10). The excess of fractures in people on rosiglitazone was mainly upper limb (RR 1·57, 1·12–2·19, p=0·0095) and distal lower limb (RR 2·60, 1·67–4·04, p<0·0001), and was mainly in women (RR 1·75 upper limb and 2·93 distal lower limb). Hip and femur fracture did not increase with rosiglitazone treatment; a non-significant excess in small numbers of spinal fractures was noted.

Discussion

The aim of the RECORD trial was to assess the overall cardiovascular safety of rosiglitazone, when added to metformin or sulfonylurea treatment, compared with that of an active control of standard dual therapy, metformin plus sulfonylurea.[13] The primary endpoint included cardiovascular death or any cardiovascular hospitalisation during follow-up, which occurred in 321 people of the rosiglitazone group and 323 of the active control group. The trial had less statistical power than initially planned because the overall primary event rate in the 4447 patients followed for a mean of 5·5 years was substantially lower than that anticipated in the protocol power calculation, for reasons previously discussed.[18] Nevertheless, the CI for the primary endpoint's HR excluded the predefined 20% excess risk, thereby satisfying the criterion of non-inferiority.

Two predefined sensitivity analyses—a per-protocol analysis on randomised dual therapy and one excluding certain primary endpoints not of atherosclerotic origin—gave similar findings. Within-strata analyses also gave similar findings when comparing rosiglitazone with metformin, and rosiglitazone with sulfonylurea, all in combination with the other background therapy.

Previously recognised increased risk of heart failure with thiazolidinediones is confirmed in our study.[12,21,22] Here, the risk was doubled with rosiglitazone compared with active control (61 *vs* 29 cases, p=0·0010), indicating an excess of one heart failure event per 385 person-years. Because these events resulted in hospitalisation and because the number of deaths for heart failure increased, at least in some cases thiazolidinedione-associated heart failure is not benign.

The prespecified secondary composite endpoint of cardiovascular death, myocardial infarction, or stroke was similar for patients on rosiglitazone or active control (154 *vs* 165 cases, table 4). However, debate on the possible effects of rosiglitazone on myocardial infarction has been extensive after the publication of the revised European licence in 2006 and the Nissen and Wolski report in 2007.[16,17,23,24] In the RECORD trial, we had an excess of eight cases of myocardial infarction (both fatal and non-fatal) in the rosiglitazone group, which gives rise to an HR of 1·14 with a wide CI, which is not statistically significant. Therefore, the evidence regarding a potential risk of myocardial infarction of patients on rosiglitazone compared with that of controls is inconclusive; however, if a risk exists, it is low and does not increase the fatality rate (table 4). This risk is in comparison with agents that gave reductions of myocardial infarction in the UKPDS.[17,25]

	Rosiglitazone (N=2220)	Active control (N=2227)
Deaths		
All cause	136	157
Cardiovascular death	60	71
Sudden death	8	12
Myocardial infarction	7	10
Heart failure	10	2
Stroke	0	5
Other acute vascular event	1	5
Other cardiovascular mortality	6	4
Unattributed cause*	28	33
Cardiovascular hospitalisation	288 (483)	284 (490)
Invasive cardiovascular procedures	85 (99)	100 (116)
Myocardial infarction	60 (66)	52 (57)
Stroke	46 (51)	63 (67)
Heart failure	57 (69)	29 (36)
Atrial fibrillation	35 (39)	36 (47)
Angina pectoris	25 (31)	26 (29)
Unstable angina pectoris	24 (28)	24 (28)
Transient ischaemic attack	10 (10)	10 (10)
Amputation of extremities	5 (6)	15 (23)
Other	71 (84)	66 (77)

Data are all events not just first events, and so may add up to higher numbers than those given in table 4. *Fatal events of unknown cause were regarded as being of cardiovascular origin, unless evidence existed to adjudicate them otherwise.

Table 5: **Patients with events (numbers of events) for various cardiovascular hospitalisations or deaths**

In the rosiglitazone group, there were 17 fewer strokes than in the active control group (46 *vs* 63 cases), which corresponds to a non-significant risk reduction of 28%. Stroke was significantly reduced by treatment with rosiglitazone by around 50% in a combined analysis of all early trials.[16]

Both all-cause deaths (136 *vs* 157) and cardiovascular deaths (60 *vs* 71) were somewhat fewer in the rosiglitazone group, but neither difference was statistically significant (table 4). The significant excess of deaths due to heart failure in the rosiglitazone group is compatible with overall increased risk of heart failure. It is offset by a similar observed reduction in deaths from stroke and other acute vascular events in the rosiglitazone group.

Findings from prespecified subgroup analyses of the primary endpoint were unremarkable, except for a possible, but not statistically significant, increased risk for cardiovascular events for patients on rosiglitazone with previous ischaemic heart disease (figure 4). The excess relative risk for heart failure was similar for people with and without previous ischaemic heart disease. In

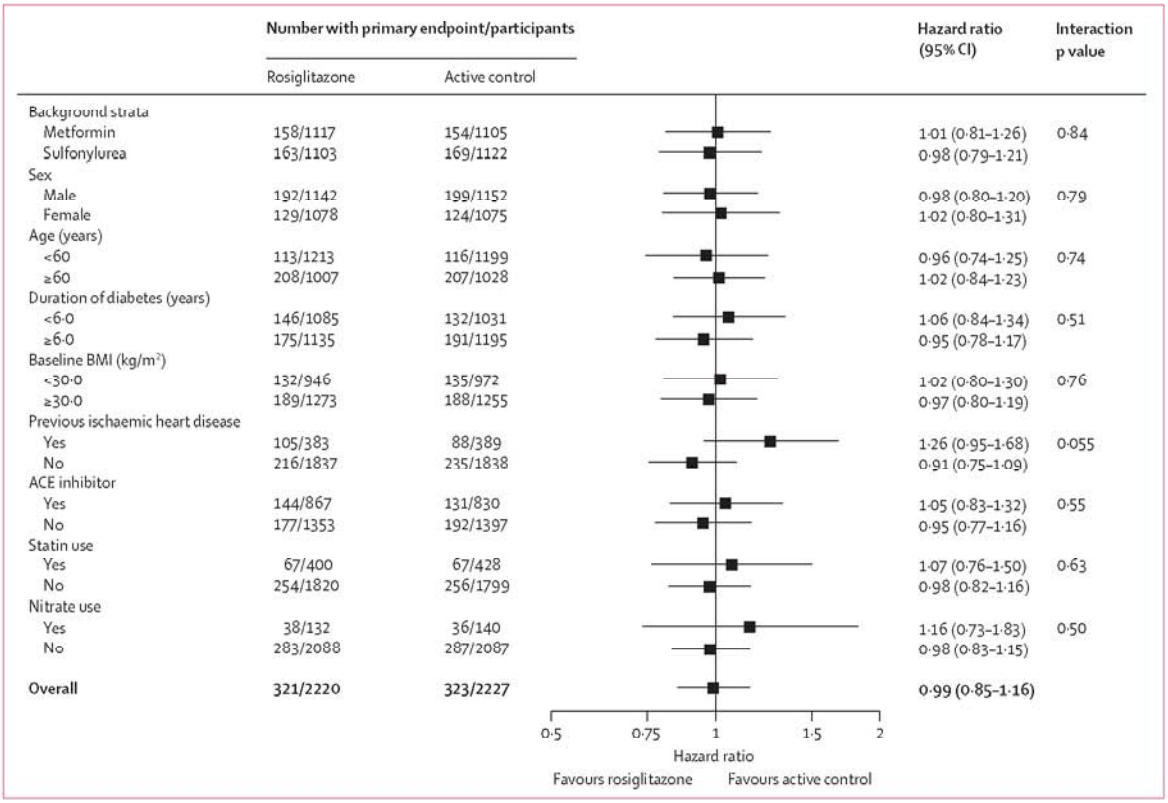

Figure 4: **Hazard ratios for the primary endpoint on the basis of prespecified subgroups according to particular baseline characteristics of interest**
ACE=angiotensin-converting enzyme. BMI=body-mass index.

people with previous myocardial infarction or angina, there was no excess of cardiovascular events with rosiglitazone compared with control medications.

Changes in cardiovascular risk factors over 5 years show evidence of superiority of rosiglitazone with regard to blood glucose control compared with both metformin and sulfonylurea (table 2), which is in line with a previous long-term monotherapy trial.[26] However, the rosiglitazone group had higher serum LDL cholesterol (but also higher HDL cholesterol) than had the active control group, and greater bodyweight gain at 5 years.

Data from UKPDS suggested that monotherapy with metformin in an obese subpopulation was beneficial compared with conservative management: RR for myocardial infarction was 0·61 (0·41–0·89) at planned study end.[7,25] However, in a smaller study, metformin added to sulfonylurea seemed to increase diabetes-related death, with an unchanged risk of myocardial infarction.[7] In the ADOPT study, in which cardiovascular events were not adjudicated, sulfonylureas were associated with lower rates of cardiovascular outcomes, whereas metformin and rosiglitazone were similar.[16,26] Here, we found in the two strata separately that rosiglitazone is similar in combination therapy for risk of cardiovascular events to both metformin and sulfonylureas. Therefore, the implication is that all three medications affect overall cardiovascular outcomes similarly.

The ADOPT study raised the issue of distal fractures in women.[19] Our study shows that the increased risk of fractures seems confined to upper limb and non-femur/hip lower limb fractures, and is mainly in women (table 7). Although our data might be reassuring regarding the issue of osteoporotic hip and spine fractures, longer follow-up in a higher-risk population, such as the elderly, is probably warranted before drawing any conclusion.

No overall difference in the incidence of malignancies was recorded, including for bladder, prostate, breast, or colon cancer. The group treated with rosiglitazone had a reduced incidence of pancreatic cancer, but this might have happened by chance. A suggestion of increased pneumonia with pioglitazone in the PROactive trial is not confirmed for rosiglitazone.[12] Data are available from adverse-event reporting on macular oedema, with a possible increase of non-serious events in patients treated with rosiglitazone.

Some potential weaknesses of the study might have had an effect on the conclusions. The greater use of loop diuretics in the rosiglitazone group than in the control group might have decreased the rate of heart failure, although the increased use might have been because of heart failure. Similarly, the rate of arteriosclerotic events in the rosiglitazone group might have been reduced by greater statin use than in the control group (9·2% higher at 5 years), although in both groups statin use was below

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	Rosiglitazone (N=2220)	Active control (N=2227)	p value
Infections	139 (6·3%)	157 (7·0%)	0·32
Pneumonia	41 (1·8%)	35 (1·6%)	0·56
Malignancies	126 (5·7%)	148 (6·6%)	0·20
Prostate cancer*	15 (1·3%)	21 (1·8%)	0·41
Breast cancer*	11 (1·0%)	17 (1·6%)	0·34
Colon cancer	10 (0·5%)	14 (0·6%)	0·54
Pancreatic cancer	2 (<0·1%)	13 (0·6%)	0·0074
Bladder cancer	6 (0·3%)	5 (0·2%)	0·99
Gastrointestinal disorders	133 (6·0%)	119 (5·3%)	0·39
Myocardial infarction	74 (3·3%)	67 (3·0%)	0·59
Myocardial ischaemia	14 (0·6%)	10 (0·4%)	0·54
Unstable angina	39 (1·8%)	38 (1·7%)	0·99
Angina pectoris	48 (2·2%)	37 (1·7%)	0·27
Coronary artery disease	24 (1·1%)	33 (1·5%)	0·29
Atrial fibrillation	33 (1·5%)	34 (1·5%)	1·00
Heart failure	82 (3·7%)	42 (1·9%)	0·0003
Cerebrovascular accident	43 (1·9%)	63 (2·8%)	0·064
Transient ischaemic attack	22 (1·0%)	25 (1·1%)	0·78
Hypertension	19 (0·9%)	21 (0·9%)	0·89
Pulmonary embolism	10 (0·5%)	13 (0·6%)	0·68
Bone fracture†	49 (2·2%)	36 (1·6%)	0·18
Osteoarthritis	29 (1·3%)	24 (1·1%)	0·58
Non-cardiac chest pain	21 (0·9%)	19 (0·9%)	0·89
Hyperglycaemia	27 (1·2%)	55 (2·5%)	0·0027
Hypoglycaemia‡	15 (0·7%)	6 (0·3%)	0·076
Macular oedema‡	0 (0·0%)	0 (0·0%)	..
Cataract	17 (0·8%)	13 (0·6%)	0·57
Anaemia	16 (0·7%)	10 (0·4%)	0·32

Data are number of patients (%). Data are for serious adverse events reported for more than 20 people or those predefined as being of particular interest in the context of thiazolidinedione therapy. *For prostate cancer, data are for men only, and for breast cancer data are for women only. †For non-serious adverse events and details, see table 7 and text. ‡For non-serious adverse events, see text.

Table 6: Patients with serious adverse events

	Women		Men		All	
	Rosiglitazone (N=1078)	Active control (N=1075)	Rosiglitazone (N=1142)	Active control (N=1152)	Rosiglitazone (N=2220)	Active control (N=2227)
All	124 (154)	68 (78)	61 (71)	50 (54)	185 (225)	118 (132)
Upper limb	63 (78)	36 (39)	23 (23)	19 (19)	86 (101)	55 (58)
Distal lower limb	47 (49)	16 (17)	23 (24)	11 (11)	70 (73)	27 (28)
Femur/hip	7 (8)	7 (7)	3 (3)	1 (1)	10 (11)	8 (8)
Spine	8 (8)	4 (4)	6 (6)	5 (5)	14 (14)	9 (9)
Pelvis	0	1 (1)	0	3 (3)	0	4 (4)
Other	11 (11)	10 (10)	14 (15)	15 (15)	25 (26)	25 (25)

Numbers are participants (events). Some participants had more than one fracture and in different areas of the body.

Table 7: Bone fractures reported as serious and non-serious adverse events

that recommended as part of good clinical management for diabetes.[4,27] However, because statins reduce arteriosclerotic events by 25%, the HR could have been reduced by no more than 2%, which would not alter the conclusion of non-inferiority.

The study also had limited statistical power for individual components of the primary endpoint because it was never intended to answer these questions. Furthermore, the overall cardiovascular event rate was lower than anticipated at the time of trial design, limiting the scope for reliable exploratory analyses. Nevertheless, non-inferiority for the primary endpoint was still achieved because the point estimate of the HR was close to 1·00. Whether myocardial infarction and stroke are worsened or improved by treatment with rosiglitazone compared with metformin or sulfonylurea is not clear, but mortality is not increased.

Although this study was open label, in-depth site and data inspections in some countries did not suggest any bias in reporting. Non-compliance and other biases in study conduct might have been an issue after the publication of the Nissen and Wolski report in 2007,[17] but publication of the interim RECORD data analysis and the statements of the study's data safety and monitoring board convinced investigators and participants of the ethics and safety of continuing the study.[18] Loss of participants during follow-up is inevitable in a large multicentre international long-term clinical trial. In the RECORD study, this loss was low for vital status (2·0% person-years of follow-up), but the number of people withdrawing from study visits was greater (7·2% person-years of follow-up).

Strengths of the study include the blinded endpoint adjudication and recruitment of a clinically representative population from various countries across Europe and Australasia. Internal data checks did not indicate geographical variation or that the background strata represent populations from different regions. Additionally, blood glucose control at baseline and during the study, although on average worse than desirable levels, was not unrepresentative of usual practice. The comparators used were glucose-lowering drugs that are cardiovascular protective[17,26] and are alternative agents of choice when prescribing rosiglitazone,[4,27] providing a strong clinical context for interpreting the findings.

What are the clinical implications for the future use of rosiglitazone? Rosiglitazone is not recommended for people with a history of heart failure or with previous problems that might have led to myocardial dysfunction. Rosiglitazone should be used with caution in women at high risk of fractures. Although our evidence is insufficient to rule out a small increased risk of myocardial infarction caused by rosiglitazone when compared with other glucose-lowering agents, rosiglitazone does not increase overall cardiovascular morbidity or mortality.

Contributors

All members of the steering committee named as authors (except JJVM) were involved in the design of the study. PSC provided statistical advice. The report was drafted by PDH, SJP, and NPJ, who had access to the data and who were able to check its analyses. All authors took part in the revision of the report.

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(Wetzlar), A Schaffert (Stuttgart), C Raddatz (Gau-Algesheim), D Ayasse (Kallstadt), R Naumann (Chemnitz), G Scholz (Offenbach), P Kirrbach (Burgstaedt), O Mueller (Lambrecht). *Greece (135)* S Raptis (Athens), E Pagkalos (Thessaloniki), S Pappas (Piraeus), A Fragkoulia (Patra), N Katsilambros (Athens), A Melidonis (Athens), G Piaditis (Athens), C Zoupas (Athens), K Soulis (Thessaloniki), A Vagenakis (Patra), D Makriyannis (Ioannina), P Kaldrimidis (Athens), I Migdalis (Athens). *Hungary (400)* M Baranyai (Szombathely), P Faludi (Budapest), I Földesi (Szentes), B Gachályi (Budapest), M Dudas (Gyula), I Hidvégi (Gyor), E Juhász (Eger), Z Kerényi (Budapest), G Neuwirth (Debrecen), T Oroszlán (Zalaegerszeg), J Pátkay (Dunaujvaros), K Simon (Siófok), J Szegedi (Nyiregyhaza), G Tamas (Budapest), J Mészáros (Nyiregyhaza), G Vándorfi (Veszprem), P Voros (Budapest), G Kurta (Berettyoujfalu). *Italy (116)* C Fossati (Milano), L Uccioli (Roma), R Pasquali (Bologna), N Melchionda (Bologna), M 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M Macko (Presov), J Fabry (Bratislava), I Buganova (Zilina), L Fabryova (Bratislava), L Kalinova (Bratislava), J Dzuponova (Prievidza), B Krahulec (Bratislava), E Toserova (Bratislava), Z Nemethyova (Bratislava), J Vozar (Samorin), A Gabrisova (Trencin), I Tkac (Kosice), J Okapcova (Banska Bystrica), T Kupcova (Lucenec), E Nehajova (Kysucke Nove Mesto), P Farkas (Sahy), E Martinka (Lubochna). *Spain (64)* M Muñoz Torres (Granada), L Escobar Jimenez (Cadiz), I Conget (Barcelona), J Herrera Pombo (Madrid), S Gaztambide (Bilbao), J Manzanares (Reus), A Serrano (Vizcaya), C Vazquez (Barcelona). *Sweden (467)* M Schönander (Göteborg), A Norrby (Göteborg), R Tengel (Skene), A Nilsson (Helsingborg), I Lager (Kristianstad), U Mathiessen (Oskarshamn), P O Andersson (Eksjö), U Adamsson (Danderyd), F Sjöberg (Linköping), E Forbes (Nacka), L Nicol (Köping), S Lindmark (Umeå), D Aronsson (Mora), M Dahl (Kungälv), M Landin-Olsson (Lund), B Polhem (Uddevalla), P Hellke (Göteborg), J Waller 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Conflicts of interest

PDH, SJP, HB-N, RG, MH, MK, and JJVM, or the institutions with which they are involved, receive funding for research, educational, and/or advisory activities from pharmaceutical companies, including GlaxoSmithKline, and in some cases from the manufacturers of sulfonylureas and metformin preparations and other competing products. PSC and NPJ are employees of, and hold stock in, GlaxoSmithKline.

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